OCCUPATIONAL TUMORS AND ALLIED DISEASES

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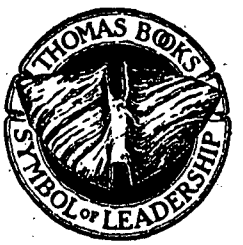
OCCUPATIONAL TUMORS AND ALLIED DISEASES

OCCUPATIONAL TUMORS AND ALLIED DISEASES

By

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This book is dedicated to the memory of those of our fellow men who have died from occupational diseases contracted while making better things for an improved living for others.

PREFACE

THE amount of factual information and the scientific as well as practical significance of tumors of occupational origin have increased rapidly during the past two decades. This development, however, so far has not found an adequate and comprehensive presentation in the medical textbooks dealing with industrial diseases or with cancerous growths. There is thus a place and a need for a separate and detailed treatise on occupational blastomas and related diseases.

It is the principal aim of this book to furnish an extensive source of information concerning the various aspects and the different types of these neoplastic disorders which have come to claim an ever-increasing importance as a part of the problem of cancer in general. A reference book is now offered in which the pertinent data, often not readily accessible and widely scattered in journals, books and separate communications of a diverse character, have been compiled. An attempt is made to analyze critically and to integrate the evidence obtained from different sources, and to correlate and evaluate the various observations made and theoretical conceptions advanced, so as to form a well balanced and, when possible, coherent picture of the subject under discussion.

The treatise may appeal and serve, therefore, as a guide to all those directly or indirectly interested in and charged with the supervision of industrial and public health hazards or concerned with the diagnosis and treatment of neoplastic diseases. The book is addressed to the

a) medical profession, particularly those of its members who are engaged in the clinical management and scientific study of cancer and of occupational diseases, including their medico-legal aspects.

b) governmental agencies charged with the safeguard of public health, the supervision of working conditions in industry and commerce, and the sanitary control of the various types of merchandise, especially foodstuffs, wearing apparel, drugs, cosmetics and the innumerable chemicals contained in articles used in the household, agriculture, etc.

c) legislative bodies formulating the laws which regulate the activities of the above mentioned governmental agencies, and of the private parties concerned with occupational hazards causing the production of industrial cancers.

d) workmen's compensation boards, industrial commissions, etc.

e) legal and judicial profession.

f) industrial managers and engineers.

g) life insurance and accident insurance companies.

h) research workers in biology, chemistry and physics.

An appreciable unevenness exists in the presentation of the various aspects of the individual occupational neoplasms. This is in part due to the fact that marked differences exist regarding the amount of information available for any particular type of tumor, and in part to the irregularity with which our knowledge has progressed at different times and at various points. The apparent great complexity of the subject matter, the existence of an appreciable number of disconnected or controversial observations, and the rapid and continuous expansion of the borders of our knowledge, may necessitate not only modifications in the interpretations of observations recorded, but also demand that final judgment must be suspended on certain points until some future time.

The extensive bibliographies conform to the reference character of the book. A fairly complete list of references is offered for the majority of industrial neoplasms discussed. A restricted number of publications, selected according to their relative scientific or practical value or because of some special feature, is given with those industrial tumors for which a very abundant literature exists. The bibliographies, in these cases however, are also of great fullness and representative in character. No attempt has been made to cover the literature comprehensively, which has been accumulated concerning the traumatic causation of neoplasms, as a great number of publications dealing with the subject are of little value.

It is obvious that in the difficult task of collecting data from many sources and about widely differing aspects, errors or omissions may have occurred. The indulgence of the reader is asked in this matter and the hope is expressed that his suggestions and criticisms may assist in remedying such defects and in improving the work in the future.

I wish to express my sincere gratitude to William R. Warner & Company, Inc., and especially to Mr. G. A. Pfeiffer, President, and Dr. Marvin R. Thompson, Director of the Warner Institute for Therapeutic Research, for the continued interest shown in the progress of this work and for the encouragement extended to it until its ultimate publication.

W. C. H.

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OCCUPATIONAL TUMORS AND ALLIED DISEASES

[I]

CONCEPT AND SIGNIFICANCE OF OCCUPATIONAL TUMORS

1. THE NEW ARTIFICIAL ENVIRONMENT

THE great majority of disease conditions results from an interaction of the cells of an organism with some animate or inanimate, exogenous, environmental agent. Until the early part of the nineteenth century the general knowledge concerning the nature and causative mechanism of these etiological factors was highly deficient for most of the diseases known to occur up to that time. The deep ignorance prevailing in such matters was hidden behind the vague concept of miasma.

A fundamental change in this deplorable condition was brought about during the latter half of the past century through the discovery and subsequent intense study of the numerous pathogenic micro- and macro-organisms, such as bacteria, protozoa, viruses, and worms. Since then, and until rather recent times, the chief interest and energy of medical research has been expended upon the elaboration and accumulation of data regarding the characteristics and properties of, and the pathogenic effects produced by, these animate constituents of our natural environment.

The remarkable achievements contributed in this respect by the various and, in part, newly developed branches of medical science (clinical medicine, bacteriology, parasitology, immunology, pathology, physiology, pharmacology, and hygiene), aided by the simultaneously rapidly advancing basic sciences of chemistry and physics, have led to the institution of protective, preventive and therapeutic measures controlling effectively a great number of the formerly dreaded and often fatal or disabling infectious diseases.

However, during the same period in which these noteworthy advances concerning the animate pathogenic environment were made, a revolutionary change in our inanimate, external environment took place through the development of modern industry and the general use of its products in daily life, transforming thereby the former state of an agricultural civilization into an industrialized one.

While the inanimate, exogenous environment, to which man and animals are exposed, depended through the preceding ages mainly upon the locally prevailing geological and climatic conditions determining the type of fauna and flora and represented in this sense a part of the natural environment, the gigantic growth of modern industry occurring in its main portion within the lifetime of men now living, i.e., within the last one hundred years, has intro-

duced numerous artificial, heretofore unknown, exogenous factors in constantly increasing number and variety. The creators and beneficiaries of the industrial development are thereby made potential victims of health hazards which cause numerous and diverse acute as well as chronic and insidious diseases never observed before. This powerful impact of the rapid rise of modern industry upon the inanimate exogenous environment affects mainly and primarily the industrially employed parts of the present-day population, but extends also to a considerable degree upon practically all other portions of the population and influences all branches of human activity, including personal and public hygiene, nutrition, clothing, living quarters, habits and customs (Zangger).

The rise of industrialization during the past century has vastly expanded the production and use of formerly known substances and manufactured goods and has resulted as well in the manufacture of innumerable new ones, entailing the employment of new techniques of production, handling, and consumption, and necessitating the application of many new physical and chemical agents. There have appeared entirely new methods and means of power production, transportation, communication, lighting, heating, water supply, disposal of industrial wastes and municipal sewage, road construction, printing and illustration, food production, processing of foodstuffs, clothing, mining, metallurgy, and other forms of industrial production.

The chemical industry especially has excelled in the creation of this new artificial environment by producing new synthetic substances in never-ending number and for ever-increasing purposes (dyes, mordants, explosives, plastics, fertilizers, insecticides, fungicides, solvents, rubber, resins, lacquers, pigments, paints, finishes, textile fibers, fuel and lubricants for motors and machines, refrigerants, building materials, radioactive substances, food components, drugs, toilet articles, pharmaceuticals, household supplies, and innumerable other articles.

The introduction of air pressure tools, air pressure chambers, biologically highly active rays (roentgen-rays, radium rays, ultraviolet rays), the use of airships and airplanes, etc., has widened greatly the influence of occupational conditions of a physical nature upon the health of the modern industrial worker.

The growth of metallurgical establishments has brought about an intensified utilization of the various metallic natural resources, many of which were unknown and never before used for industrial purposes, such as aluminum, magnesium, chromium, nickel, vanadium, and radium. This has increased the number of potential health hazards, and also is responsible for a greatly augmented exposure of the industrially employed as well as general population to substances of marked toxicity, such as arsenic, lead, mercury, antimony, manganese, chromium, and radium, used industrially or released as waste products into the environmental air (carbon monoxide, sulfur dioxide, arsenious

oxide, etc.), or into the waters of lakes and rivers (phenols, arsenicals, etc.) serving as water supply of adjoining communities.

Additional sources of chemical pollution of water supplies can be traced to the discharge of wastes from chemical factories, paper plants, cellulose manufacturing establishments, gas works, rayon plants, textile dyeing plants, tanneries, etc., and to the introduction of tarry substances from freshly tarred or oiled roads with the rain water, or of arsenicals used for the spraying or dusting of fields, orchards, and woods, or released from copper and iron smelters into the air and carried down by the rain. The use of chemical insecticides on fruits and vegetables containing lead, arsenic, copper, nicotine, etc., and the employment of numerous organic and inorganic chemicals in the processing of foodstuffs for various purposes (preservation, coloring, consistency, etc.) have added greatly to the number of exogenous agents composing this new artificial environment whose biological effect upon the human organism is often unknown or little appreciated.

This very incomplete list of new environmental agents may suffice as an illustration of the degree and character of the changes which the inanimate exogenous environment has undergone during the last five to ten decades (Dublin; Zangger; Koelsch; Johnstone; Sappington; Martland; Martineck; Aikman; Goodman and Sulzberger; Williams; Störring; Ruf and Fluck; Jephcott; Voss; Baader; and many others). While thus the factors composing the old natural environment are still present and active to some measure in a more or less modified form, the agents constituting the new artificial environment are superimposed upon them to an increasing degree, not only producing diseases of purely industrial origin but, through interaction with the pathogenic influences of the natural environment, also giving rise to disorders of complex etiology.

The immediate and great significance which this situation possesses from the standpoint of medical care and public health is reflected to some extent in the legislative measures taken in various countries in the form of food and drug acts and industrial health laws as well as in the increasing interest industrial diseases have aroused in the medical profession in recent years. It must be admitted, however, that these reactions can be considered only as *the first steps* toward an adequate and general appreciation, knowledge and control of health hazards which have arisen as the result of this industrialization and which produce diseases neither properly understood nor recognized in an appreciable number of instances.

The situation existing in this respect is less alarming with regard to the acute industrial poisonings than to the chronic poisonings, especially those of metatoxic type. It is in general neither very difficult to determine the nature of the various causative agents responsible for the majority of the acute industrial poisonings nor is it hard to recognize the etiologic character of the symptomatic manifestations produced by them, because of the special circum-

stances which, as a rule, surround such events. The often rapid onset of impressive symptoms following a usually accidental exposure to rather massive amounts of a particular agent of known toxic qualities furnishes in general the conclusive evidence.

The various possible sources of acute poisonings are obvious in well conducted industrial establishments when medically properly supervised, where adequate precautions for prevention under ordinary working conditions, as well as appropriate therapeutic facilities in case of their accidental occurrence, are provided. It must be noted, however, that less favorable conditions are apt to exist in this respect in plants which employ only a small number of men or where products with proprietary names and of unknown chemical nature are handled. Serious difficulties in regard to a correct and prompt diagnosis of acute industrial poisonings may be encountered in those cases in which the initial symptoms are rather mild and uncharacteristic, while being followed only after a more or less prolonged period of delay by manifestations of more severe nature.

It is obvious that the diagnostic obstacles offered by chronic poisonings are often greatly magnified, as the symptoms elicited by a prolonged exposure to comparatively small amounts of toxic agents are not infrequently neither characteristic nor appreciable for a varying period and may be considered even as "insignificant" from a medical standpoint, especially in the presence of metatoxic effects. Serious manifestations appear in many instances only after many months, or years, of exposure, or may be noted only many years after cessation of exposure to the injurious agent. The proper recognition of the causes and symptoms of many of these medically as well as socio-economically highly important diseases occasioned by the agents of the new artificial environment represents one of the chief problems with which the medical profession, public health agencies, industrial managements and legislative bodies will be confronted in the near future. At the present time, an appropriate progress, which may be considered as commensurate with the already existing tremendous significance of these environmental diseases, is obviated by various factors.

There exists among the members of the medical profession an inadequate knowledge and appreciation of these sources of disease conditions and of the symptoms produced by these environmental agents. In addition to the lack of proper training in this respect during the years devoted to medical education, the average physician has little opportunity to familiarize himself with the nature and possible biological action exerted by the multitude of substances used, produced or handled in the various industrial operations. His patients employed in such establishments are frequently not able to provide him with reliable or adequate data upon inquiry, while the plant management may be reluctant to divulge such information to a physician not connected with the industrial organization.

Environmental diseases of industrial origin present, moreover, not infrequently marked diagnostic difficulties, as an appreciable number of these disorders may masquerade symptomatically under the disguise of known infectious diseases or are readily and often complicated by such conditions, so that the primary, occupational, etiological aspect becomes obscured.

Some industrial diseases, on the other hand, exhibit symptoms simulating closely those found in certain diseases of unknown etiology (so-called "idiopathic diseases"), or are mistaken for organic changes observed with the "physiological" aging of the organism. The following examples may serve as illustrations of these points:

The occupational exposure to benzol and to certain benzol derivatives may lead to the development of a great variety of *hyperplastic and hypoplastic reactions* of the blood and blood-forming organs resembling in many respects those caused by some infectious, endocrine, or unknown agents. *Certain disorders of the central and peripheral nervous system* which are elicited by contact with a great number of industrial poisons (carbon monoxide, hydrogen sulfide, carbon disulfide, chlorinated aliphatic hydrocarbons, aromatic hydrocarbons, organic and inorganic compounds of lead, mercury, arsenic, manganese, etc.) may mimic closely those accompanying infectious diseases or appearing as degenerative manifestations of unknown etiology (Baader). The inadequate knowledge as to the existence of such causal connections is the reason that the industrial factors producing nervous disturbances often remain unappreciated, resulting in the institution of ineffective therapeutic measures and in the complete omission of essential preventive procedures. The causal role which an occupational exposure to noxious gases and vapors (sulphur dioxide, nitrous oxide, etc.) as well as to various kinds of organic and inorganic dusts (manganese, soot, iron oxide, and especially silica) plays in the production of *chronic inflammatory conditions of the respiratory organs*, is not rarely more or less obliterated by the secondary onset of a bacterial infection, for which the industrial agent has prepared the soil. The occurrence of *peptic ulcers* in individuals exposed to carbon disulfide vapors is generally little considered in the diagnosis of gastric disorders. Likewise is the production of degenerative and fibrosing lesions of the liver by aliphatic chlorinated hydrocarbons, aromatic hydrocarbons, etc., not taken into account in determining the causation of *cirrhosis of the liver*. A considerable number of *irritative or allergic cutaneous lesions* occurring among the industrially occupied, as well as among the general population, can be traced to an exposure to some of the innumerable new chemical compounds employed in industry and incorporated in articles of every-day use. These manifestations are not infrequently mistaken for bacterial or fungal infections which, however, are often superimposed upon, or activated by, the chemical agents.

Apart from these medical difficulties which impair the proper advancement in the knowledge and recognition of these environmental diseases there exists a fundamental and serious lack of information concerning *the biological effects exerted by many of the new synthetic compounds*. While the manufacturers of such chemicals, as well as the users of new and old substances for new purposes,

are usually well acquainted with, or anxious to determine over a wide range, the various chemical, physical, and technical properties of these agents, they do not, in general, feel obliged, or consider it apparently less important, to conduct equally thorough and detailed investigations in regard to the possible injurious effects which their products may produce in the human organism, prior to their introduction into large scale industrial operation or before they are offered for sale to the public.

This increase in the number and types of industrial and environmental diseases following upon the rise of the modern and artificial environment furnishes the background for the prominence which occupational neoplasms and related hyperplastic cellular responses of exogenous origin have now attained. Industrial tumors and allied diseases constitute an integral part of the pathological reactions resulting from the change which the inanimate environment has undergone during the past century (Teutschlaender). While a few of the industrial cancers have been known or have existed without correct recognition prior to the advent of the modern industrial era (pulmonary cancers of the Schneeberg and Joachimsthal miners, scrotal cancers of the chimney sweeps and arsenic workers in England), the great majority of the occupational blastomas appeared after the start of modern industrial development. In fact, the overwhelming number of occupational neoplasms has been placed on record during the last forty years. During this period there was not only a constant rise in the absolute number of these disorders, but also a marked increase in their organic types and in the exogenous sources. It must be pointed out, however, that the different occupational cancers participated in a very irregular fashion in this evolution. While some of them regressed in frequency in practically all countries in certain occupations, such as roentgen cancer of the skin among the medical profession, after the hazard had been properly appreciated and adequate precautionary and preventive measures had been instituted, they did not take the same course in other occupations into which they had more recently gained access to an increasing degree.

Other industrial neoplasms, such as aniline cancers of the urinary bladder, exhibited a decreasing incidence in some countries in which their development was originally favored by special industrial conditions (Germany, Switzerland), and where effective preventive measures were first developed. On the other hand, the same cancers appeared with increasing frequency during more recent years in other countries (England, Italy, United States), following the establishment of etiologically important chemical industries.

The promoters and managers of such newly developed manufacturing industries apparently neglected to profit from other countries' adverse experiences. It may be noted that the technical changes which resulted in an amelioration of the industrial cancer situation in some instances were prompted mainly, until rather recent times, by a desire of plant management to reduce

production costs and to improve the quality of the manufactured goods for sales reasons, and were not instituted primarily to provide better working conditions and protection to the workers.

The variations which the numerical and organic incidence of industrial neoplasms have displayed in recent decades and in different countries and industries, reflect, to a certain extent, the general and local growth of modern industrial enterprises. It may be conceded that occupational risk represents only one of several predisposing causes of cancer which may be operative in different instances or under different circumstances, as it is not uncommon to find in occupations an excessive mortality from cancer in certain sites for which no apparent explanation can be found in the industrial risks (Young and Russell). While it may be possible that in some occupations the excessive indulgence of habits, like smoking and drinking, may play a predisposing role, this conception should not be unduly encouraged in view of the serious ignorance existing concerning the cause or causes of cancer in general and industrial cancer in particular. Past experiences suggest that such observations regarding an unexplainable high organic incidence of cancer in certain professions can be traced more likely to an industrial source than to habit factors.

The medical, medico-legal, sociological, and scientific significance of occupational tumors extends far beyond the limited importance these proliferative reactions possess as an industrial disease. Industrial neoplasms are, at present, with the exception of a few tumors of non-occupational, environmental origin, the only blastomas in man of which the approximate cause is known. Occupational cancers represent, because of this fact, a challenge to the industry as well as to public health agencies, as they are the only malignant neoplasms the development and occurrence of which can be largely or completely eliminated, if proper precautionary measures are taken to prevent any undue contact of the workers with the offending agents, or if the cancerigenic factors are excluded from industrial operations (Hoffman, W. J.; Hoffman, Fr. L.).

Occupational cancers have attained additional importance as the study of these neoplasms has resulted in the discovery and synthesis of a large number of chemical carcinogens (dibenzanthracenes, cholanthrenes, etc.), some of which were found to be closely related to substances occurring normally in the body (bile acids, sex hormones), or forming constituents of our food and our cells, such as cholesterol and vitamin D. (Kennaway; Cook; Hieger; Cramer; and others [England]; Fieser and coworkers; Shear; Andervondt; Loeb; and others [United States]; Butenandt [Germany]; Yoshida and coworkers [Japan]). Occupational cancers have thus furnished the basis for one of the greatest advances ever made in the knowledge of cancer in general.

Inasmuch as the crude cancer death rate has markedly increased in all civilized countries, the increase in the United States being nearly 65 per cent between 1900 and 1933 (Rector), and considering the fact that cancer ranks now second as a cause of death, killing every tenth individual dying after the

age of forty years, any addition to existing information on the causation and causative mechanism of cancer is a highly important matter. This statement receives additional emphasis from the fact that in spite of definite advances made in the diagnosis and therapy of malignant diseases, and in spite of the increased cancer-consciousness of the general public, there has not been noted any appreciable reduction in the rate of cancer mortality (Wood). The far-reaching practical significance of the study of industrial cancers is derived from the light which such investigations shed upon the importance of preventive measures in the fight against cancer and upon the causes and causative mechanism responsible for these growth manifestations.

2. DEFINITION AND CLASSIFICATION OF OCCUPATIONAL TUMORS

The term "occupational tumor" is applied to blastomatous reactions originating in individuals during the course, and as the result of, the regular and usually prolonged exercise of certain occupational activities entailing contact with some exogenous, physical or chemical, carcinogenic agent acting in proper intensity. These occupational neoplasms proper are caused in general by specific factors which form an integral part of ordinary working conditions. They must be distinguished from accidental occupational tumors which result from or follow upon some extraordinary, unforeseen, accidental injury sustained while at work. The blastogenic factors allegedly responsible for these accidental neoplasias are of nonspecific nature, and consist primarily and usually of a single or repeated physical or chemical trauma unrelated to regular occupational influences.

Occupational tumors thus represent a variety of the environmental neoplasms, i.e., blastomatous responses to the action of certain specific extraneous cancerigenic factors of natural or artificial origin. The existence of non-occupational environmental cancers provides not only additional proof of the importance of exogenous agents in the causation of malignant and benign growths, but represents also a material source of information for the study of occupational blastomas. Non-occupational environmental tumors and related manifestations are, like the occupational variety, the result of extraneous influences of various kinds, such as *habits* (carcinoma of the oral cavity in betel nut chewers; carcinoma of the skin of the abdominal region in carriers of kangri [Kashmir] or kairo [Japan]); carcinoma of the penis due to uncleanliness and the use of caustic therapeutics in Chinese; *customs* (keloids in colored races caused by decorative scarring); *climatic factors* (skin cancers among light pigmented inhabitants of dry and sunny regions [Australia, Argentina, Midwestern States]); *geological influences* (cancer of the skin among inhabitants of areas in which the water supply is contaminated by arsenic from arsenic-containing ores [Silesia, Argentina]); adenomas and carcinomas of the thyroid among inhabitants of regions in which endemic goiter occurs because of *iodine deficiency of the soil* (Switzerland, Great Lakes

region); *endemic parasitic infections* (cancer of the bladder due to schistosomiasis in Egypt; primary cancer of the liver in many tropical and oriental countries caused by endemic helminthic infestations). Similar observations as to the occurrence of environmental blastomas on the basis of endemic infections with worms and viruses have been made in a number of animals (rats, rabbits, monkeys, frogs, fishes, chickens).

A tumor, in order to be classified and acceptable as of occupational etiology, must fulfill two conditions:

1) The clinico-statistical evidence must show that the incidence rate of a tumor of a certain type and site is appreciably and significantly in excess among workers engaged in a particular operation entailing contact with a more or less well-defined agent, of the rate observed for the general population. Proper consideration must be given in such an analysis to the relative age distribution and cancer incidence in the two groups compared, for the purpose of excluding not only the possibility of an apparent, age-conditioned excess, but also for determining whether younger age groups are more greatly affected in the occupational groups than in the general population, as a shift of the peak of incidence of a particular cancer into younger age groups favors an exogenous and specifically occupational influence operative in its genesis. Additional evidence of clinico-statistical nature supporting an occupational causation of a particular tumor may be obtained, if it can be demonstrated that a high, while not always statistically significant, incidence increase of the particular cancer exists among those workers who have either less intimate contact with the suspected agents, while working in the same operation, than the individuals most often affected, or who are employed in the environmental zone and thus sustain only an indirect and less intense exposure. Circumstantial evidence of this nature has been considered as sufficiently conclusive in numerous instances for extending official medico-legal recognition to neoplastic conditions of occupational origin before ultimate proof of such an etiology has been provided by a successful experimental reproduction of the particular neoplasm in animals.

2) The existence of adequate experimental evidence possessing conclusive value is essential not only from a scientific viewpoint, but is of decisive influence in all those instances in which the clinico-statistical data are not quite definite and permit, therefore, merely suggestive conclusions.

In the establishment of adequate and reliable clinico-statistical, as well as experimental associations, certain difficulties have to be overcome or taken into account to insure accurate results. Inasmuch as the information obtainable from death certificates is usually not only deficient, but also notoriously unreliable, especially as to the cause of death, it is indispensable that the diagnosis of the neoplastic nature of an allegedly occupational disease is based, in at least the great majority of cases investigated, upon the results of histo-pathological examinations of the suspected new growth. Similarly, uncertainty must be eliminated concerning the matter of occupation. Data

regarding the latter must be defined accurately, as there occur not only marked variations in the intensity of exposure to certain occupational agents among the members of the same occupation, but also among those employed in the same operation. An additional source of error may enter into the clinico-statistical studies by the tendencies of workers to change their occupation during the course of life and thus to become exposed to occupational hazards of varying nature, while the death certificate usually lists only the last occupation engaged in. In view of this fact and considering that occupational neoplasms have, as a rule, a long latency period extending over 40 years or more in instances, it appears of utmost importance that reliable data on the occurrence, sources and incidence of occupational neoplasms must be based on the entire occupational history of workers suspected of having industrial tumors.

In appraising the relative value of the experimental reproduction of a particular industrial neoplasm from a scientific as well as medico-legal standpoint, consideration must be given to the fact that any occupational tumor is, by its very nature, equivalent to an unintentionally produced experimental tumor in man. The clinico-statistical evidence thus may provide under favorable circumstances, as convincing proof of the occupational origin of a tumor as that which can be supplied by its experimental reproduction. The great and immediate significance of a successful experimental reproduction of occupational neoplasms in animals consists for this reason often not so much of a conclusive demonstration of a well-defined, industrial etiology, but of furnishing a suitable and practical method for the intelligent study of their causes and causative mechanisms. It must be emphasized in this connection that only positive experimental results possess conclusive value, while a negative outcome of experimental approaches frequently holds the problem merely in abeyance. Whereas failures in this respect may be caused occasionally by the use of an improper, noncarcinogenic agent, incorrectly suspected as the causative factor, past experiences have shown that negative results followed not infrequently upon the employment of the actual causal agent under unsuitable experimental conditions (insufficient intensity and duration of exposure, improper administration of agent, selection of a completely or markedly refractory species, etc.). It is a well-established observation that the reactivity of different species to some carcinogenic agents varies considerably and may influence, therefore, decisively the outcome of experiments of this kind.

Occupational neoplasms can be classified into certain groups according to the relation which the site of a particular occupational tumor possesses to the type of contact with a given carcinogenic agent:

1) Direct contact tumors.
   a) Cutaneous neoplasms caused by a direct local action of mineral oil, crude paraffin, creosote, anthracene, solar rays, ultraviolet rays, roentgen-rays,

rays from radioactive substances upon the cellular components of the skin.

b) Pulmonary blastomas resulting from the exposure to and inhalation of radio-active material, chromates, asbestos, nickel carbonyl, tarry substances.

c) Tumors of the nasal passages and sinuses following upon the exposure to radioactive substances, chromates, nickel carbonyl.

d) Cancers of the upper alimentary tract exhibit statistically causal relations to certain industrial cancerigenic agents acting most probably directly upon the mucous membranes of these passages.

2) Excretory contact tumors.

a) Epithelial neoplasms of the skin following the ingestion of arsenicals.

b) Blastomas of the urogenous tract resulting from an exposure to certain aromatic amines, excreted in the urine.

c) Cancers of the liver, intestinal tract, female genital organs provide, theoretically, a possibility of proliferative manifestations of this type.

3) Depository contact tumors.

a) Cancers of the skin associated with the deposition of arsenicals in the cells of this organ.

b) Sarcomas of the bony tissues following the storage of radio-active material in the bones.

4) Tumors in tissues possessing a special affinity or sensitivity to a particular cancerigenic agent.

a) Blastomatoid and blastomatous reactions of the hematopoietic tissues following an exposure to roentgen-rays, radioactive substances, benzol, and chemically related substances.

b) Cancers of the urinary bladder and liver caused by an infestation with certain helminthic parasites exhibiting an affinity to these organs.

It is in the nature of any classification of biological manifestations that the dividing lines between the different groups are not always sharp and that a certain amount of overlapping occurs, or that several factors are operative and combine in bringing about a neoplastic response in a particular case. Thus, arsenicals are not only deposited and stored in the skin, but they are also excreted through its various component parts (epidermis, hairs, sweat). A depository and excretory mechanism may, therefore, be active in the development of arsenic cancers of this organ. Malignant neoplasms of the lung, on the other hand, may be elicited not only by a primary contact with radioactive substances inhaled in the form of gases or dust, but may also be caused by the exhalation of gaseous members of this chemical group representing degradation products of solid radioactive substances which may originally have entered the body through the mucous membranes of the digestive or respiratory tract.

The nature of the ensuing neoplasms depends moreover on the type of contact with a particular carcinogenic agent. Radioactive substances may thus produce cancers of the skin following a prolonged localized exposure to the rays emitted by these chemicals, while osteogenic sarcomas may result when these chemicals are deposited in the bony tissue, pulmonary neoplasms when

they are inhaled, and leukemias when a generalized exposure of the body to these substances exists. Similarly, the leukemic action of benzol may not entirely be an expression of a specific cellular affinity of the myeloid marrow cells to benzol, but it may be, in part, a product of an accumulation of this chemical in the fat tissue composing the bone marrow (Schrenk).

In addition to the definitely precancerous and cancerous lesions, occupational health hazards may produce a large number of proliferative reactions displaying more or less blastoma-like, or blastoma-near, qualities. Manifestations which belong to this group of tissue responses to exogeneous, occupational agents are transitory and reversible erythrocytoses and leucocytoses, sometimes associated with heterotopic hyperplastic proliferations of the corresponding hematopoietic tissues, adenomatoid hyperplasias of the liver accompanying an industrial cirrhosis of this organ, and similar reactions of a regenerative, compensatory or irritative nature. Nonspecific, traumatic, occupational influences are especially active in the production of such conditions (traumatic epithelial cysts caused by tissue misplacement, sarcomatoid granulomas, metaplasias of various kinds, traumatic ossifying myositis, Dupuytren's contracture, ganglions, keloids, warts, etc.).

The accidental occupational tumors may be grouped as follows:

1) Tumors following upon a single trauma resulting in
   a) an acute formation of a neoplasm.
   b) a delayed development of a blastoma.
2) Tumors following after repeated injuries of nonspecific, but sometimes occupational nature.
3) Tumors preexisting at the time of the traumatic episode, but aggravated in their further course by the accidental injury.

Specific occupational cancerigenic influences and non-specific traumatic accidental factors sometimes combine in eliciting a neoplastic reaction, or in modifying the time of its manifestations, or in affecting its course (mechanical or chemical trauma acting on a chronically roentgen-injured skin; thermic burn in a skin having chronic tar dermatitis with precancerosis, etc.).

An intermediate position between occupational tumors proper and accidental occupational neoplasms is occupied by those blastomatous reactions which arise, apparently or allegedly, as the result of a prolonged or repeated action of nonspecific occupational influences, of physical or chemical nature, causing a chronic traumatization or irritation of the tissues.

3. HISTORICAL, INDUSTRIAL AND GEOGRAPHICAL ASPECTS

Already the writings of Andreas Vesalius (1543) and of Peter von Forest contain allusions that certain occupations may be related to the formation of tumors (Ullmann, K.). Bernardino Ramazzini (1700) seems also to have entertained similar thoughts (International Labour Office Reports). However, not until much later were such vague suspicions placed on a firmer and factual

basis, when Percival Pott (1775) advanced good evidence connecting the appearance of scrotal cancers in chimney sweeps with their occupational exposure to soot. The number of recognized occupational cancerigenic agents, and of occupational neoplasms, has increased steadily since then, especially during the last five decades. A few of the diseases accepted among the occupational neoplastic disorders (pulmonary cancer of the miners of Schneeberg and Joachimsthal in Saxony and Bohemia, respectively) have been known symptomatically for several hundred years, others (carcinoma of the urinary bladder due to infections with Schistosomum haematobium among the fellahs of Egypt) possibly even for several thousand years without their actual nature and etiology being recognized.

Following the description of the first occupational cancer, almost four decades passed before a second source of industrial neoplasia was discovered. Ayrton in 1820, and Paris in 1822, recorded the frequent occurrence of scrotal carcinomas among the workers employed in the copper and tin smelters of Cornwall and suggested the existence of an etiological relationship between these lesions and the occupational exposure to arsenic fumes. Of these two occupational tumors belonging to the pre-industrial era, the cancer of the chimney sweeps is still observed in England, while the arsenic cancer of the copper and tin smelters in Cornwall has been extinct for many decades following the cessation of these operations.

Fifty more years elapsed, and the industrialization of the western and central European countries had been in full swing for several decades, before the first occupational neoplasm was described which can be called a product of this modern development and of the new artificial environment. In 1875, von Volkmann reported the first three cases of occupational paraffin cancer of the skin in workers employed in the newly-established lignite industry in Saxony. Only one year later (1876) Bell made a similar discovery among the paraffin workers of the shale industry of Scotland, and Manouvriez placed the first cases of tar and pitch cancer of the skin on record, which were observed among the workers of a patent fuel plant in France. The neoplastic nature of one of the oldest occupational tumors, the bronchial carcinoma of the Schneeberg miners, was established in 1879 by Härting and Hesse. Ten years later, Derville and Guermonprez called attention to the occurrence of skin cancers among the workers of crude oil refineries in northern France. In 1893, Unna described the cutaneous cancers in sailors which were attributed by Dubreuilh (1896) to the action of an excessive solar irradiation. During the preceding year (1895) Rehn made his first report on the excessive incidence of cancers of the urinary bladder ("aniline cancer") among the workers of the German dye industry, which had been established about thirty years previously. Thus, within twenty-five years, six new sources of industrial malignancy were added to the list of occupational tumors before the turn of the century. Four of these six sources were outgrowths of the industrial development.

Since that time a great many new types of industrial neoplasms have been placed on record. In 1902, the first case of roentgen-carcinoma of the skin was recorded by Frieben and Albers-Schönberg. The presence of a causal interrelation between vesical Bilharziasis and bladder carcinoma was noted by Ferguson in 1911. In the same year von Jagič, Schwarz, and von Siebenrock reported the first cases of leukemia attributable to chronic exposure to roentgen-rays. The last addition to this list before the World War was made by Rambousek in 1913, who observed the occurrence of cutaneous malignancies among workers handling crude anthracene oil.

Following this event Leitch and Sequeira described, in 1920, the first case of cutaneous malignancy caused by an occupational exposure to radioactive substances. Two years later, Southam and Wilson added the occupational carcinomas of the skin occurring in mule spinners in England resulting from the contact with certain lubricating oils. In 1924, Cookson placed creosote upon the list of occupational carcinogenic agents responsible for the development of epitheliomas of the skin. The occurrence of leukemia referable to the chronic occupational exposure to benzol was noted by Delore and Bergamo in 1928. During the following year, Löwy finally succeeded in placing the centuries old pulmonary diseases prevalent among the uranium miners of Joachimsthal among the occupational malignancies, while Martland added, in 1931, osteogenic sarcomas to the list of malignant neoplasms caused by an occupational exposure to radioactive substances. Alwens called attention to the high frequency of pulmonary cancer in chromate workers in 1932, while Bridge and Stephens recorded cancers of the nasal passages and of the lung among the workers employed in certain nickel refineries. The occurrence of pulmonary carcinomas among the employees of plants and laboratories handling radioactive substances was noted by Neitzel in 1935. During the following year, Kawahata described the high incidence of pulmonary malignancies among workers of generator plants who were exposed to the inhalation of hot tar fumes. After Wood and Gloyne (1934) as well as Lynch and Smith (1935) had reported the occurrence of pulmonary cancer in workers of asbestos plants, Horning, in 1938, claimed, when noting several new cases of this type, that causal relations exist between pulmonary asbestosis and the subsequent development of malignancy of the lung.

This chronological enumeration of the various occupational cancers, according to the different etiological factors and sites, reflects clearly the recent marked increase in the incidence of these industrial disorders. This fact is brought out still more strikingly by the continuous spread of these neoplastic diseases among the workers of an increasing number of different industries producing, using, or handling known carcinogenic occupational agents, and among the workers of such industrial establishments in different countries to the degree in which they participated in the modern industrial development.

The marked expansion of occupational contact with carcinogenic agents

upon new branches of industry is well illustrated by the wider distribution of tar and pitch cancer upon the various industrial groups of workers. While these occupational neoplasms were observed primarily among men employed in briquette factories, they have been seen later among workers of gas plants, tar distilleries, cork stone plants, manufacturers of dry battery cases, calkers of boats, road construction and repair men, fishermen and sailors, etc. Similarly, oil and paraffin carcinomas, found originally in workers of oil refineries, in mule spinners, employees of lignite and shale distilleries, have made their appearance in engineers, mechanics, oilers of machines, gunsmiths, employees of the automobile production and service trades, etc. Whereas arsenical epitheliomas were described first in smelters of tin and copper, they have now been seen in workers manufacturing or handling sheep dip, insecticides, arsenical pigments, agricultural laborers, silver miners, and among other workers with arsenicals. While other industrial cancers exhibit similar, but less striking developments, there remains the peculiar fact that the absolute number of occupational neoplasms is relatively low in comparison with cancers of unknown etiology, in spite of greatly increased occupational contact with carcinogenic agents. Then, too, many industries in which such exposures are definitely or probably present have failed to record any cases of occupational neoplasia.

This observation permits several explanations. The inference can be drawn that the actual existence of such neoplasms has not been recognized, or has been disregarded and has not been made property of public knowledge. The great discrepancies in the extent and character of the laws on industrial health prevailing in different countries may account readily for at least a part of those occupational blastomas which have escaped public recording. There exist, on the other hand, marked variations in production methods, in type and extent of precautionary and protective measures and medical supervision, as well as in the nature of the basic material used for the manufacture of identical or dissimilar end products. These variations are of sufficient significance to influence the incidence or appearance of occupational blastomas in different factories, industries and countries. Oil cancers of the skin, for instance, are particularly frequent in England because of the widespread use of a lubricating oil prepared from Scottish oil shale in certain industries. Similarly, the occurrence of cancers of the nasal passages, and of the lung in workers employed in nickel refineries, has remained so far restricted to Wales, apparently because of the use of refining methods, adapted to certain nickel ores. A special type of coal, the use of fireplaces and the existence of tortuous and narrow chimneys, together with special cleaning methods and bad hygienic conditions, seem to represent the etiological complex responsible for the prevalence of scrotal cancer in chimney sweeps in England. Chromate cancer of the lung as well as pulmonary malignancy among miners of radioactive ores have been observed thus far only in Germany. The reasons under-

lying this localized occurrence, however, are not clear, as similar occupational conditions seem to exist in the corresponding industries of several other countries.

The marked variations in the distribution, type and size of industrial establishments in different countries represent an additional important cause for the varying geographic incidence of occupational tumors. Highly developed industrial countries, such as England, Germany, Switzerland, Italy and the United States, possess a comparatively large number and more different types of industrial neoplasms than countries which are more agricultural (Denmark, Holland, Hungary, and Sweden, for example). The unusually low incidence of occupational neoplasms recorded in highly industrialized countries, such as Belgium and Japan, constitutes probably an apparent exception from this rule. As the industrial development in Japan is of relatively recent date, industrial cancers have been observed there only since the last ten years (Koinuma, 1931). Nagayo and Kinosita (1940), on the other hand, attributed the extreme rarity of industrial cancers in Japan, particularly among the workers employed as oilers in the textile industry, or in gas, tar, and tar by-products manufactures, to the fact that Japanese workers are very clean, taking a hot bath daily and change clothes frequently, thereby lowering the intensity of exposure. The cause for the scantiness of occupational neoplastic manifestations among the industrially active population of Belgium is not readily apparent. It may be possible that a certain deficiency in the number of post-mortem examinations as well as in the control of industrial health conditions plays a role in this respect, because medical surveys conducted recently among workers employed in Belgian pitch and tar plants revealed the occurrence of a considerable number of tar and pitch cancers during the last few years (Uytdenhof; Firket and Malter). An extraordinarily low rate of industrial tumors is reported also from France and Luxemburg, both countries possessing a very well developed industry.

There are a few additional factors which exert a certain influence upon the regional distribution of occupational cancers. Racial factors, for instance, contribute to the incidence of skin cancer in regions having an intense solar irradiation and being inhabited by members of light pigmented races. Industries located in countries where colored labor is available for operations entailing the contact with tarry and oily substances, on the other hand, are apt to show a low incidence of occupational tar and oil cancer, as the skin of Negroes is less susceptible to such reactions than that of white people. Occupational cancer caused by endemic parasitic infections (bladder cancer on the basis of Bilharziasis) displays also a locally restricted occurrence (Egypt). Similar considerations apply to industries depending upon the occurrence of rare minerals (radio-active substances [Schneeberg, Joachimsthal]).

No encouragement, however, can be given to the reasoning advanced by Hoffman (1928) in an attempt to explain the existence of marked variations

in the incidence of occupational neoplasms in different countries. This investigator contended that the scarcity of recorded industrial cancers in the United States was attributable to the fact that the workers in America are unusually intelligent and susceptible to educational influence; that they desire to know the truth and facts of a given situation and frequently govern their conduct accordingly; that this observation applies to no class of workers more than to those who are connected with the chemical industries in which malignant growths are unusually frequent in other countries. It is idle to speculate on, or argue about, the relative intelligence and self-reliance of industrial workers of different countries and their alleged influence upon the incidence and prevention of occupational malignancy. Then, too, it is more than doubtful whether American chemical workers are more thoroughly informed concerning the biological properties of the substances they come in contact with, or have a better opportunity to acquire such information, than their colleagues in other countries. But this is certain, the chemical industry of the United States has contributed its fair share or even more than that to the number of "recorded" industrial cancers. Hoffman's claim is highly objectionable, as it is apt to produce a spurious feeling of safety and superiority, which is especially ill placed in view of the fact that adequate industrial health legislation and laws on occupational diseases in many states of our country are of very recent date, or still non-existent.

4. STATISTICAL RELATIONSHIP BETWEEN OCCUPATION AND GENERAL CANCER INCIDENCE

The general and increasing interest in the problem of malignant neoplasms, prevailing since several decades, has fostered relatively early statistical investigations into the relative incidence of cancer in various occupational and social groups (Braithwaite; Newsholme [1881-1890, England]; Connel [United States]; Behla [1908]; Wolf; Weinberg; Aschoff [1887-1899]; Loth [1900]; Karupp; Gollmer [Germany]). Aschoff, as well as Loth, found a rather high mortality from cancer, especially epithelioma of the skin, among gardeners, which Loth suggested was caused possibly by contact with chemical fertilizer or by parasitical infection contracted from infested soil. Similarly, a high cancer mortality among English and Hungarian farmers was noted by Braithwaite and Jacobs, respectively, while Newsholme's analysis put this occupational group into second place as to relative cancer mortality, the highest place being occupied by chimney sweeps, where the ratio was found to be 70:156.

Connell, on the other hand, listed farmers in eighth place, with workers, sailors and fishermen, smiths, nurses, clergymen, servants, and masons preceding them, and merchants and gardeners following them in the order of relative incidence of cancer deaths. In the statistical studies reported by Behla, members of the literary profession exhibited the highest cancer mortality. They

were followed by members of the clothing trades, sanitation and medicine, lumber trades, etc., the farmers being well in the middle of the list, and workers employed in metallurgic, chemical, building and mining industries having the lowest cancer death rate. Oliver, in 1902, stated that glass makers, ironstone miners, tin miners, wool workers, shoemakers, and especially chimney sweeps display an excessive mortality from cancer, while miners in general were found to have a death rate 16 per cent below the average.

These few examples of the early efforts in this field may suffice, as the results obtained were not only contradictory (Jacobs), but the analyses were made without proper consideration of age groups and site of neoplasms, and were for this reason unreliable (Arnstein). Staemmler characterized these studies as defective and primitive beginnings in the establishment of interrelations between occupational exposures and cancer susceptibility by the statistical method. In commenting on these data, Koelsch called attention to several additional factors which made the information conveyed by these early investigations untrustworthy and misleading.

This investigator pointed out that it is difficult to obtain representative occupational groups, that is, groups of individuals exposed to the same occupational conditions to approximately the same degree and duration. A group such as "metal workers," for instance, includes persons having the most varied contact not only with different metals and metallic compounds, but also with numerous other substances, such as silica, lubricants, chemical fumes, and gases of varying kinds. Thus they form a group of individuals which is by far too crude and comprehensive for any significant and reliable statistical evaluation.

Similar, and perhaps even stronger, objections can be raised against the group of "chemical workers," as this is composed of individuals exposed to an even much greater number of substances possessing the most varied biological properties and acting at the same time under very different conditions and intensities upon the individual members of this group. Statistics on general cancer incidence, as well as organ cancer incidence based on an occupational grouping of such vagueness, are not infrequently absolutely valueless.

In addition to the lack of proper consideration given in these early studies to the age grouping in different professions, to the sites of the tumors and to the sex of the workers, practically no attention has been paid to the fact that many workers, especially the unskilled type, exhibit a more or less definite tendency to change the nature of their occupational activities. The inclusion of such workers and their relative proportion in the different occupational groups introduce additional sources of error, because these individuals are listed, as a rule, in that occupational group to which they were attached when the malignant neoplasms were first noted or to which they belonged at the time of their death. There are, moreover, certain non-occupational factors, such as condition of living quarters, diet, habits, hobbies, customs, and regional

and social influences which may play a more or less important role in the causation of malignant diseases occurring in members of the different occupational groups.

In spite of these adverse critical observations, the different groupings and standards used and the wide variations in the results obtained in the various statistical studies of this early period (Behla [Prussia, 1907-1908]; Kolb [Bavaria, 1905-1908]; English statistics, 1900-1902; data of the Sickness Insurance Company of Leipzig, 1887-1901, and similar investigations from Norway, Austria, Hungary, and the United States), general agreement seems to exist on the point that agriculturists exhibit a higher cancer mortality than industrially employed workers. Professions with a relatively high cancer mortality, according to Koelsch, are day laborers and maids, individuals employed in agriculture, forestry, lumber industry, hostelries, smiths, textile plants, governmental offices, and clergy, while a low cancer incidence is recorded for persons employed in mines, stone quarries, metallurgic industry, navy, and army. Inasmuch as not only the age grouping, but also the possible influence of non-occupational exogenous factors, vary greatly for these occupational classes, Koelsch concluded that the general statistical occupational studies made before and during the first decade of the present century were practically valueless.

There exist more recent statistical analyses dealing with the relationship between occupational activity and cancer morbidity and mortality; they come especially from English sources. In these some of the objectionable features of the older statistics are more or less absent. According to these studies, covering the period 1921-1923, the following occupations showed a high cancer mortality in England: wood workers, butchers, millers, dealers in liquors, barmen, stone masons, and chemical workers, while a low death rate from cancer was observed for soldiers, sailors, compositors, etc. (International Labour Office Reports).

A very comprehensive and thorough statistical survey as to the cancer mortality in the different trades and professions was made in England by Young and Russell (1926), based on an evaluation of 46,118 death certificates of the Registrar General of the years 1910, 1911, and 1912, giving sex, age, specific trade, and cause of death. These investigators divided the population for this purpose into 8 social classes and found the cancer death rates for these classes shown in the table at top of page 22.

The investigators concluded that special groups of workers show significant differences in cancer mortality. Thus, textile workers have a lower cancer incidence, and agricultural workers a still lower one, while miners (mainly coal miners) have the lowest cancer mortality among the eight social groups studied. Young and Russell believe that the statistical differences observed are of significance, if the data from which they are derived can be considered trustworthy. Similar marked differences in cancer mortality were demonstrated

Social Class	Standardized Death Rate for Persons Above 15 Years	Life Table Death Rate from Cancer
I. Upper and middle class	1.337	2.142
II. Intermediates	1.269	1.965
III. Skilled workmen	1.396	2.051
IV. Intermediates	1.283	1.957
V. Unskilled workmen	1.701	2.050
VI. Textile workers	1.397	1.864
VII. Miners	1.082	1.512
VIII. Agricultural workers	0.965	1.796
Coal miners	1.069	1.497
All males occupied and retired	1.355	1.983

by these investigators from an examination of the different trades and professions.

The comparative mortality figure (1910-1912) from cancer of all males in Wales was found to be 78, that of zinc manufacturers 178, barmen 137, patent fuel manufacturers 131, beer bottlers and cellarmen 126, brewers 125, messengers, watchmen and porters, as well as brass and bronze workers, 118, slaters 116, seamen and railway workers, each 110, tobacco manufacturers 38, coke burners 40, lithographers, tallow, soap and glue manufacturers each 41, printers and machine compositors 43, straw plait and hat manufacturers 44, clergy 45, maltsters 47, electric supply workers 49, plate layers 50. As the total figures available for zinc manufacturers, patent fuel manufacturers, coke burners, straw plait and hat workers, and electric supply workers were too small, the information obtained as to the cancer incidence in these groups was regarded as statistically unreliable.

It may be mentioned that Young and Russell also noted marked and significant differences in the mortality from cancer of various sites (skin, lip, tongue, esophagus, stomach, bowel, bladder, and larynx) related to certain trades and professions. In a study of the occupational incidence of cancer of the penis and of the scrotum in the general population by Kennaway (1928), this investigator also employed 8 social or occupational groups in his analysis (1. chimney sweeps; 2. textile workers; 3. all persons not included in 1 and 2, but especially likely to be exposed to carcinogenic agents such as tar, pitch, lubricating oils [workers in tar, patent fuel, coke and its by-products, fishermen, boatmen, drivers, stokers, and cleaners of engines]; 4. metal workers [may possibly also be exposed to lubricating oil]; 5. coal workers [miners above and below ground at the pit, coal boat loaders, trimmers]; 6. all manual occupations; 7. clerical and light manual workers; 8. agricultural workers).

Kennaway observed that the ratio of scrotal cancers to cancers of the penis is lowest in the class of agricultural laborers, whereas in the remaining classes

the ratio is lower in clerical workers than in manual workers and is lower in those doing light, than in those doing heavy, manual work. He suggested that cancer of the scrotum affects especially the classes who wash least and are most exposed to the dust of towns.

Two valuable statistical analyses on the occupational incidence and distribution of cancer were made in the United States, the one by Hoffman, the other by Haagensen (1931). Hoffman tabulated the deaths from cancer of the male generative organs (scrotum and penis) for twenty-three occupational groups according to the data obtained from the Bureau of Vital Statistics of the United States Census.

CANCER DEATHS—MALE GENERATIVE ORGANS
U. S. Registration Area—1926–29 (Hoffman)

	Penis		Scrotum	
	Deaths	Per Cent	Deaths	Per Cent
1. Laborers	131	18.4	22	16.5
2. Farmers	141	19.8	21	15.8
3. Gardeners	3	0.4	—	—
4. Fishermen and sailors	5	0.7	1	0.8
5. Army and navy	2	0.3	—	—
6. Transportation	25	3.5	1	0.8
7. Commercial and clerical	50	7.1	19	14.3
8. Professional	41	5.8	5	3.7
9. Machinists and mechanics	19	2.7	5	3.7
10. Textile	5	0.7	8	6.0
11. Painters	10	1.4	1	0.8
12. Blacksmiths	7	1.0	—	—
13. Carpenters	21	3.0	2	1.5
14. Plumbers	3	0.4	1	0.8
15. Shoemakers	5	0.7	—	—
16. Tailors	4	0.6	—	—
17. Bakers	2	0.3	1	0.3
18. Butchers	4	0.6	—	—
19. Printers	7	1.0	—	—
20. Miners	11	1.5	3	2.2
21. Chauffeurs	5	0.7	—	—
22. Electricians	7	1.0	—	—
23. Miscellaneous	72	10.1	23	17.3
24. Unknown and retired	130	18.3	20	15.0
	710	100.0	133	100.0

The occupational distribution of scrotal cancer, as recorded by Hoffman, shows much less variation than cancer of the penis. Nevertheless, there is a

definite parallelism between the absolute incidence of scrotal and penile cancer in the different occupational groups, the reason for which, however, is obscure. Hoffman felt that it is unlikely that social factors, such as special uncleanliness allegedly prevailing in certain occupational groups, would account for the high frequency of scrotal as well as penile cancer among laborers, farmers, commercial, and clerical workers.

Analyzing his data for the influence the state of marriage played in regard to incidence, Hoffman made the surprising observation that both types of cancers are significantly more frequent in married males than in unmarried males over 15 (scrotum: married 1.1, unmarried 0.4, per one million; penis: married 6.1, unmarried 1.9). Hoffman's studies of occupational groups on the basis of 3,462 deaths from cancer among males during the years 1920-27 (San Francisco Cancer Survey, Seventh Report, Prudential Press, 1931) did not render any significant information that would connect any particular occupation with some special type and site of cancer.

Haagensen made statistical studies regarding the significance of the occupational factor on the incidence of skin cancer, especially of the penis and scrotum, among various occupational groups. He attempted to obtain more definite information by applying the following formula:

$$\frac{O}{P} \times P_m = E.$$

In his calculations H represents the population of New York, Jersey City and Newark; P is number of occupied in Metropolitan area; P_m is the total number of males with skin and mucocutaneous cancers listed by occupation on the records of the Memorial Hospital; O stands for the number of males in a particular occupational group; A is the actual number of patients from the occupational group in question; E is the expected number of cases. Haagensen reasoned that if the morbidity of cancer is the same in all occupational groups the expected number for the Memorial Hospital records could be expressed in the formula given. A and E are then compared and the percentage of excess or defect determined. The statistical significance of the data thus obtained can then be ascertained by ordinary statistical calculations.

With this procedure Haagensen found that a high excess of penile and scrotal cancer existed in machinists and mechanics occupationally exposed to lubricating oil. This observation confirmed a finding previously made by Young and Russell, who reported a high incidence of penile cancer among equally exposed millwrights, turners, fitters, etc.

There was, moreover, an excess of skin cancer in brick and stone masons in Haagensen's as well as in Young and Russell's statistics, which was attributed by the English investigators to an occupational exposure to solar rays and mechanical trauma. Occupational factors of physical or chemical nature (sun light, tar, etc.) are blamed by Haagensen for the highly excessive incidence of skin cancer observed among sailors and boatmen (420 %), locomotive

engineers (900%), gardeners (800%), fishermen (600%), and roofers (500%).

No plausible explanation of this type, on the other hand, could be proposed by Haagensen for the excessive frequency of cutaneous malignancy among janitors, sextons, clergymen, blacksmiths, painters, glaziers, and varnishers, as none of these groups showed an equally extraordinary susceptibility in the English statistics. It is remarkable that occupational groups, such as petroleum workers, and gas house workers, who are notoriously exposed to irritative and carcinogenic agents exhibited in the statistics of Haagensen only a minor or negligible excess of skin cancer (250% and 150%, respectively).

Weiss, reviewing 100,000 cancer deaths which occurred in Baden during a period of 50 years, and analyzing those 12,354 cases which were observed during the ten years preceding 1932 as to the influence of an occupational factor, found the highest liability for contracting cancer in the following occupations: smiths, flour millers, shoemakers, carpenters, brewers, artists, chimney sweeps.

While the number of statistical studies on this subject is much larger, no additional information would be obtained by citing such data. Inasmuch as the basic evidence upon which these investigations are based is taken from death certificates, the conclusions arrived at do not deserve too much trust. The best that can be said for them is that they provide in some respects presumptive and confirmatory evidence, while being unreliable and misleading in others as to the presence or absence of causal interrelationships between general or local cancerigenesis and occupational factors.

A considerable number of sources of potential errors were mentioned above, but the most serious factor depreciating the value of these studies is the use of the death certificates, in which the cause of death is recorded in most instances either on the basis of clinical medical evidence, or, which is worse, on data supplied by lay persons, such as undertakers, coroners, etc. It is a well known and often established fact that the recognition of cancerous growths in such material is often missed (20 to 40 per cent), as is evident from comparisons of the clinical diagnoses with the findings of post-mortem examinations, especially regarding to the cancers of internal organs, inaccessible to direct observation (Wells, Lubarsch, Wolff, and others).

The degree of discrepancy existing between the number of cancers recorded on death certificates and that actually present must have been more marked in former decades than during more recent ones. The reasons for this lie in the appreciable increase of the number of autopsies during this period, as well as in the fact that malignant diseases have lost more and more of the character which caused people to surround these disorders with a sort of "social" silence, and which sometimes induced physicians to falsify the diagnoses recorded in death certificates, in order to spare the feelings of the relatives.

Legislative measures taken in recent years requiring the registration of certain occupational neoplasms have contributed somewhat to the reliability of the information contained in death certificates. Nevertheless, these developments and improvements are not sufficient to make death certificates a reliable basis for the statistical study of the relationship between cancer and occupation.

It is obvious from this exposition that the statistical approach usually taken does not only supply relatively inaccurate information, but also does not prevent many occupational neoplasms from escaping recognition and recording (Carozzi). More conclusive and valuable data would be obtained, if detailed investigations and analyses were made of small, but more or less uniformly exposed groups of workers, among whom appears a slight excess in the number of certain types and especially unusual varieties of cancers from time to time, so as to determine whether such phenomena are merely coincidental in nature or related to occupational factors. The explanation is often made that isolated cases of cancer may be accounted for by the natural occurrence of the disease in the general population. This evidently follows the line of least resistance and is evidence of an irresponsible and destructive attitude in the absence of any attempt to supply proof or to adopt constructive suggestions (Henry and Irvine).

The institution of fundamental improvements in the character of the data on which comprehensive statistical analyses can be based with confidence depends upon the future introduction of certain radical changes in the governmental attitude toward this important problem of public health. It is essential that cancer be made a notifiable disease, and reportable by a statutory requirement. The official notification should contain in addition to the name, sex, race, age, and married status of the affected person, detailed data as to hereditary history, complete occupational history, habits, hobbies, diet (consumption of processed and preserved foodstuffs, especially those treated with aromatic compounds [dyes]), previous diseases and therapeutic agents used, use of cosmetics, etc.

Such a law must also convey to qualified and specially trained physicians the right to perform post-mortem examinations on all persons who were afflicted at some time of their lives by a cancerous growth. Only the establishment of accurate, complete, and reliable morbidity statistics on cancer, for which the data are collected while the affected persons are still alive and able to supply the necessary and essential information, can provide in any effective degree those data pertinent to the determination of the character and action mechanism of the environmental agents which cause cancer. Proper preventive, precautionary and sanitary measures, similar to those already in effect concerning contagious diseases, should be instituted and enforced to control this pathological manifestation of cellular growth, which has become one of the most important and urgent problems of our population structure.

The prevailing contradictory or unexplainable statistical evidence concerning

the relationship between cancer and occupational activity has given rise to the idea that other factors of a more general nature, such as environmental conditions connected with the social status or with some general extraneous factors, are of more importance in determining the variations in the incidence of cancer found in different groups of people. Brown and Mohan, as well as Heron, investigated the relationship of the social and economical status of different sections of the population to cancer incidence. Heron claimed that conditions of prosperity and culture which lead to a low birth rate were conducive also to a high cancer death rate, so that cancer incidence could not be taken as a measure of that unhealthy environment with which a high birth rate seemed to be associated.

Brown and Mohan, on the other hand, concluded from their analysis that cancer is less fatal among the higher social or economical classes; but the data on which these conclusions were based were somewhat irregular. In support of their statements, these investigators cited observations made in Hamburg, where the average income was found to be related negatively to the rate of cancer mortality. In 1923, Stevens commented that, generally speaking, there appeared to be evidence of a moderate increase in the cancer death rate down the social scale, while showing marked exceptions in favor of the very specially situated occupations of mining and agriculture. Maynard (1909) reported from American sources that the lowest death rates from cancer were observed among occupations belonging to the highest social status, while Dublin (1924) concluded, from the data of the Metropolitan Life Insurance Company (U.S.A.), that the cancer mortality rate at the ages where the cancer rate is significant decreases with the rise in the economical status.

Cramer revived, in 1927, the idea of the "social cancer" in contradistinction from the "occupational cancer." This investigator pointed out that the incidence of gastric cancer increases as one goes down the social scale, so that in the two lowest classes this type of neoplasm is responsible for two-thirds of the total cancer mortality, while it accounts for somewhat more than one-third in the highest social class. Cramer based his conclusions on data provided by statistical analyses of the cancer mortality in Bavaria (Hang, 1924-1928) for different occupations. The following tabulation by Cramer illustrates the relationships observed:

Social Class, Description of Occupation	Percentage of Gastric Cancer in Total Cancer	Absolute Number
I. Merchants, high officials, doctors	38.8	2084
II. Office workers	40.1	970
III. Publicans, brewers, small officials	48.5	2140
IV. Skilled workmen	56.8	4247
V. Unskilled workmen	63.4	2423
VI. Agricultural laborers	68.5	6907

Referring to the analyses with regard to the occupational occurrence of gastric cancer in individuals connected with the alcohol trades (Young and Russell), Cramer pointed out that some of the trades with an excessive rate of gastric cancer had no considerable exposure to alcohol consumption and that therefore the evidence implicating alcoholism in the etiology of gastric cancer was far from convincing. More recent English statistical investigations conducted on this subject (Editorial) seemed to indicate that the excessive incidence of gastric cancer in the social Class V was not caused by occupational agents, but probably by some other environmental influences. Cancers of the intestine and rectum, on the other hand, were outstanding among those cancers which exhibited for both sexes and all five social groups no definite relationship between cancer mortality and social class for persons 35 to 65 years old.

For cancers in sites most exposed to external irritation (skin, larynx, alimentary tract above pylorus), on the other hand, the cancer incidence increased continuously among the male members from Class I to Class V, while the female members did not participate in this movement (Class I, upper and middle class; Class II, intermediate; Class III, skilled workers; Class IV, intermediate; Class V, unskilled workers). Similar conclusions were reached by Stocks in 1936 from statistical data dealing with the marked variations in general and organ cancer mortality observed among the inhabitants of various parts of Wales and England. The evidence obtained indicated, in this instance, that, in addition to occupational factors, other influences of endogenous (sex, race, etc.) and exogenous nature played a role in bringing about the marked variations in the incidence of certain tumors in different localities.

The fundamental objections which can be raised against the value of these studies are identical with those previously mentioned in connection with ocupational neoplasms. Hoffman's comment, that cancer statistics related to the social and economic status must be dealt with in an extremely cautious manner if erroneous conclusions are to be avoided, must be heartily endorsed.

Variations in the incidence of cancer with regard to regions and social classes have been attributed to differences of a more general environmental nature. It has already been noted that Kennaway considered the excess of scrotal cancer among the members of the lower social classes to have been caused by a defective personal hygiene more common in the lower strata of society than among the higher ones, and to an exposure to the dust of towns.

Mention must here be made of two theories relating the higher incidence of cancer among the industrially occupied population to the production of substances released into the atmosphere, by many industrial establishments, in the form of gases or fumes, which exert their alleged specific carcinogenic influence upon the workers, as well as upon the civil population living within the fume zone of such plants. Meyers referred, in his discussion of cancer death rates, smoke, and topography, to the contention of Green, that sulfur dioxide fumes, generated in numerous industrial establishments, or resulting

from defective burning of coal in furnaces, were responsible for the excessive incidence of cancer among persons exposed to this substance for occupational or general environmental reasons (workers in aniline dye plants, paraffin factories, gas and pitch plants, breweries, metallurgical factories, etc.). The local crowding of cancer deaths in valleys, gulleys, or in such parts of the towns where uneven roof lines produced pockets in which the sulfur dioxide fumes could accumulate, was attributed by Green to this cause. From a study of three different parts of Manhattan with regard to their relative cancer death rates and environmental factors, Meyers reached the conclusion that the portions exempted or less affected by smoke, fumes, and gases had a lower cancer death rate than those in which these pollutions of the air were present. As Meyers could not trace the differences found to factors such as age, sex allocation, etc., environmental conditions of the type suggested by Green were considered to be responsible for the excessive cancer mortality in the polluted regions.

A similar conception was advanced by Stephens, who was inclined, however, to blame the inhalation of carbon monoxide, of occupational or environmental origin, for the excessive incidence of cancer in certain professions. Analyzing the cancer deaths recorded in the Registrar's General Decennial Supplement (1921), Stephens found the highest cancer mortality in occupations which he considered excessively exposed to inhalation of carbon monoxide (waiters, cutlery grinders, tin and copper miners, cellarmen, cotton spinners, hat formers, gas stokers, puddlers, and china ovenmen), while low cancer death rates were listed for occupations having little contact with this gas (ministers, clergy, bank officials, machine compositors, leather goods makers, stone miners, etc.).

These theories dealing with the nature of the various environmental agents and conditions allegedly incriminated in the causation of occupational and environmental cancer are mentioned not because they are considered as valuable and important, but as excellent illustrations of the confusion and uncertainty existing in the field of statistical cancer research. It appears to be very likely that statisticians may be able to establish many more statistically significant relationships between etiologically unrelated items, one of which being cancer incidence or etiology.

According to the existing statistical information, cancer contributes relatively little (0.9 per cent per thousand industrial disabilities per year) to the annual volume of chronic disability, owing to its low incidence. The average amount of disability per case for this disease, however, is relatively high and ranks on this basis in importance with the cardiovascular-renal diseases, nervous disorders, etc., as an important cause of industrial disability (Perott and Holland).

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[II]

OCCUPATIONAL AND ACCIDENTAL TUMORS OF THE SKIN AND ITS APPENDAGES

1. ANATOMICAL AND ETIOLOGICAL CONSIDERATIONS

THE skin and its appendiceal organs are the most common sites of occupational neoplasms, according to the information available at the present time. As the skin is the most accessible organ, this relationship is, in part, only an apparent one. The existence of a causal interrelation between an occupational exposure to a particular agent and the subsequent development of a neoplasm is recognized in this organ more readily than in any other. The principal reason for this condition, however, is an actual one and may be traced to the fact that the skin, during certain occupational activities, is not only in direct and often intense contact with extraneous, carcinogenic agents, such as tar, pitch, crude mineral oils, roentgen-rays and ultra-violet rays, but represents also an organ of excretion and storage of some carcinogenic substance, such as arsenic. These exogenous agents may enter the organism by way of the respiratory or alimentary tract.

The neoplastic effect of these various carcinogenic occupational factors to which the skin is exposed, may become manifest in the ectodermal and mesodermal components of the skin proper (epidermis, cutis), including its structurally modified portions in the external genital region (scrotum, vulva). It may involve, on the other hand, special cutaneous formations (nail beds, hair follicles) as well as the different glandular appendiceal organs (sweat glands, sebaceous glands), glomus, and nerves. In addition to these normal cutaneous structures, which may become the sites of a blastomatous response, the common congenital malformations of the skin, such as the naevi, may provide the cellular basis for the development of an industrial tumor.

It is important to note that the anatomical structure and the functional activity of the epidermis and its appendiceal organs, as well as the varying distribution of the latter elements on the different parts of the skin, determine to a certain extent the susceptibility of a particular portion to different exogenous carcinogenic agents and thus control the site, distribution and character of the ensuing tumors. The presence of a dense hair growth, as well as of an intense (normal) pigmentation, protects to some extent not only against the physical and photochemical effects of sun-rays, but mitigates the cancerigenic action of this agent. An active and abundant secretion of the sebaceous glands seems to provide a protective oily film which withstands the blastogenic

action of certain industrially used chemicals, such as tar and pitch. A dry, rugated or haired skin, on the other hand, may facilitate the cancerigenic influence of these same substances by facilitating their penetration, increased retention and prolonged contact.

It is obvious that apart from these intrinsic factors which exhibit a certain effect upon some aspects of occupational cancerigenesis of the skin, the conditions of exposure (character of the extraneous agent; direct, locally restricted external contact; more or less diffuse internal excretory or depository contact; type of occupational activity controlling site and intensity of exposure; nature and extent of protective measures) exercise a major influence upon the occurrence, incidence, distribution and type of neoplastic lesions observed in connection with the various chemical as well as physical occupational, carcinogenic agents. In view of the numerous individual, racial, occupational, climatic and other less well defined exogenous factors, great variations are observed in the geographical distribution of the various occupational cutaneous tumors.

An intimate knowledge of the character and the action mechanism of the causal agents incriminated in the production of the industrial neoplasms of the skin is of special scientific as well as of practical significance, since a great deal of circumstantial as well as direct evidence supports the contention that the same agents are active in the development of an appreciable number of non-occupational cutaneous tumors occurring among the general population. The simple listing of the various agents, recognized as the causes underlying industrial malignancy of the skin, is sufficient to demonstrate strikingly and convincingly the great probability or actual existence of such interrelations regarding the etiology of non-occupational cutaneous tumors: arsenicals (inorganic and organic), pitch, tar, soot, crude paraffin and mineral oils, creosote, anthracene, sunlight, roentgen-rays, and radioactive substances. While a non-occupational contact with some of these agents (roentgen-rays, radioactive substances) will be in general a matter of accident or carelessness, or may occur in the course of the therapeutic management of various and often non-blastomatous ailments, the exposure to others of these agents, such as arsenicals, tar and its innumerable derivatives, crude mineral oil, and creosote, has become during recent decades to an ever-increasing degree a matter of our general environment, as these substances are encountered in many articles used in our daily life for numerous purposes. Not infrequently, their presence is unknown to the consumers and users of such products who will not realize the potential danger to which they may be exposed.

Since the knowledge of the carcinogenic nature of these agents is far from being general, and considering that the carcinogenic responses may become manifest many years after the cessation of exposure to these agents, it is quite evident that the existence of causal interrelations between a previous environmental exposure to any one of the agents mentioned and the later appearing cutaneous malignant lesions is often overlooked in all probability. The recent

statement of O'Donovan concerning the striking discrepancy between the marked recent increase in the number of industrial dermatoses and dermatitis and the stationary number of industrial cutaneous cancers must be looked upon with a great deal of reservation for obvious reasons.

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GENERAL ANATOMICAL AND ETIOLOGICAL CONSIDERATIONS

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2. CHEMICAL AGENTS

A. Inorganic Chemicals

a. Arsenic—1. chemical and technological aspects

The occurrence of arsenic in nature is widespread. It is found in the ores of numerous metals (antimony, cobalt, silver, bismuth, iron, zinc, tin, lead, nickel, gold, copper) either as an impurity in an elementary form, or as a sulfide, or in combination with iron. Arsenic represents, therefore, a by-product or waste product of the smelting process of these ores. Huge quantities of arsenic fumes may be generated during these operations. Often no attempt is made to remove the arsenic from the fumes prior to their release into the atmosphere. Where this is done, the fumes are condensed in order to recover the arsenic. The condensation apparatus consists either of an extensive system of canals and chambers, in which the fumes are cooled and the arsenious trioxide is precipitated, or of an electrical appliance which is capable of freeing the waste gases of arsenic, produced during the roasting of the ores ([method of Cottrell-Möller] Ullman, F.). The crude arsenic obtained then is purified by repeated sublimation in furnaces, followed by the recondensation of the vapors formed.

This purified arsenious trioxide (As_2O_3) represents the principal arsenical from which the many other arsenic compounds are developed for manifold uses in industry, medical therapeutics and other purposes.

Arsenious oxide is employed in the glass making industry for the clearing and purification of glass (removal of carbon particles and of color resulting from the presence of lower iron oxides). This compound serves as the basic substance in the production of the various arsenicals used: (*a*) in the form of *sodium arsenite* as sheep dip (against ticks), for grasshopper bait (in Russia, South Africa, North and South America) and as an agent to destroy plant life (between railroad ties in the tropics); (*b*) in the form of *lead arsenate*, *copper arsenate* and *calcium arsenate* as an insecticide, germicide, and vermicide (rat poison) in agriculture and forestry (fruit orchards, vineyards, truck gardens, and cotton plantations). It is used in the manufacture of enamel, pigments (realgar [As_2S_2] and orpiment [As_2S_3]), Scheele's green ($CuHAsO_3$), Schweinfurt green ($Cu[C_2H_3O_2]$—$3Cu[AsO_2]_2$) employed as coloring mat-

ter in oil and water colors and paints (wall paints, wall-paper printing, cotton printing, artificial flowers, colored crayons) and as parasiticide, arsenic acid, arsenic sulfides (used for hardening of lead buck-shot).

Arsenicals are used as preservatives of pelts (taxidermy); glue (loading of yarns), as dehairing agents in the tanning industry, for the bronzing of copper and brass, in the production as well as in the fixation of aniline dyes on woven goods, in the manufacture of numerous chemicals (present as an impurity or adulterant in caustic soda, glucose, and sulphuric acid), and medicinal preparations.

Inorganic (arsenious acid [Fowler's solution], AsI_3 [Donovan's solution]) and organic arsenicals (arsphenamines, cacodylates) are contained in numerous preparations used in medical therapeutics (local caustics, tonics, antiseptics, antispasmodics, antisyphilitics) and cosmetics (hair lotions). Organic arsenicals play also an imporant rôle as war gases (Lewisite, diphenylchlorarsine).

The United States is by far the largest producer and consumer of arsenicals (Ullmann, F; *Encyclopedia Britannica.*). Considerable quantities of arsenic compounds are manufactured and used in Germany, Australia, Sweden, as well as other countries.

II. EXPOSURE

In direct relation to the widespread natural occurrence and the numerous practical uses of arsenicals, a great many individuals have a more or less intimate contact with these substances. Chronic occupational arsenicism, with or without cutaneous manifestations, is an industrial disease not infrequently encountered, provided it is searched for properly (White). Arsenicals may enter the organism by direct resorption through the skin (especially when diseased [eczema] [Deckert]); by inhalation in the form of a gas, vapor or dust; or by oral ingestion. The development of chronic arsenical dermatoses among miners exposed to dust of arsenic-containing ores has been reported by Anderson; Bayet; Schaerrer; Fischer; Eulenberg; Saupe; and others. A second group of workers, showing an especially high incidence of chronic arsenicism, is represented by men employed in the smelters where roasting, extracting and packing of arsenic is carried out (Miyaji; Paris; Saupe; Ullmann, K.). The attendants of boilers and furnaces, as well as the men shovelling the arsenic in the condensation chambers into barrels, come into intimate and extensive contact with arsenic fumes, vapors and dust. These individuals often show the local as well as the systemic toxic effects of this chemical.

Chronic arsenicism with cutaneous lesions caused by an occupational exposure has been observed during the past 70 to 80 years in workers of numerous occupations: glass workers; chemical workers (dye manufacturers, manufacturers of sheep dip); tanners; taxidermists; workers in lead factories; workers in rotogravure establishments (by the use of arsenic containing ink); workers

in oil refineries (using an arsenic containing clay); workers in oil-cloth factories; in plants producing colored paper; photographers (using arsenicals); seamstresses and weavers (handling goods dyed with arsenicals); workers in pelt and hair factories; agricultural workers; sprayers and dusters of arsenical insecticides; workers peeling fruit contaminated by arsenicals in canneries (Eve; O'Donovan; Paris; Legge; Henry; Porter; Hope; Brezina; Ullmann, F.; Fischer; Follin; Chevalier; Beaugrand; Guggenheim; Dubreuilh; Méneau; Vernois; Gaucher and Barbe; Ayres and Anderson; Simons; Blaschko; Myers, Van Dyck and Thorne; Langecker; Oppenheim; Blandet; Imbert-Gourbeyre; Bucceri; Baader; Cazeneuve; Vigne; Dörle and Ziegler; Stoeber; Schöndorf; Franseen and Taylor; McNeer; von Pein; Irvine and Turnacliff; Seyfried; Butzengeiger; and others). The intensity as well as the opportunity for an industrial contact with arsenicals have varied during this three-quarters of a century period in different occupations. While numerous chronic arsenic poisonings occurred in dye workers, weavers, and seamstresses during the early years of that period, this source of arsenicism has been reduced greatly in more recent years by the introduction of improved production methods and especially by the replacement of arsenical pigments by aniline dyes. The constantly increasing use of arsenicals as insecticides during the past 20 years, on the other hand, has opened an uncomparably wider field for occupational as well as non-occupational contact with these chemicals than has ever before existed.

The following list of workers occupationally exposed to arsenicals was published by Chamberlain (representing an adaptation of a list prepared by Dublin and Leiboff): artificial flower makers; arsenic roasters; carroters of felt hats; chargers in zinc smelters; color makers; colored-paper workers; compounders of rubber; copper founders; copper smelters; curriers in tanneries; cut-glass workers; decorators of pottery; dye makers; electroplaters; enamelers; ferro-silicon workers; fur handlers and preparers; galvanizers; gardeners; glass mixers; glaze dippers and mixers in pottery plants; gold refiners; insecticide makers; japan makers; jewelers; lead smelters; linoleum color workers; lithographers; mixers of rubber mordanters; paper glazers; paper hangers; pencil makers (working with colors); pitch workers; pottery workers; press-room workers in rubber; printers; pyrites burners; refiners of metals; rubber tire builders and workers; sealing-wax makers; sheep-dip makers; shot makers; sprayers of trees; sulphur burners; sulphuric acid workers; tannery workers; taxidermists; tinners; toy-makers; velvet makers; wall-paper printers; wax ornament workers; wire drawers; wood preservers; zinc mixers.

There are numerous additional occupations which provide a regular contact with arsenicals and represent a potential source of chronic arsenicism, arsenical dermatosis and arsenical cancer.

III. INCIDENCE OF ARSENICAL CANCER

The recorded number of occupational arsenical cancers of the skin is relatively small in comparison to the numerous cases of industrial arsenico-dermia, as the claim of Bayet and Slosse concerning the arsenical etiology of all tar and pitch cancers has been disproven definitely. The first mention and description of occupational arsenical cancer of the skin was made by Paris in 1822. This physician practised medicine in Cornwall, where at that time copper smelters and tin foundries were operated. During his professional work, Paris noticed the high incidence of cutaneous malignancy among the men employed in these factories. His description of these observations was as follows: "It may, however, be of interest and useful to record an account of the pernicious influence of arsenical fumes upon organized beings, as I have been enabled to ascertain in the copper smelting works and tin-burning houses in Cornwall and Wales. This influence is very apparent in the condition of both the animals and vegetables in the vicinity; horses and cows commonly lose their hoofs, and the latter are often seen in the neighboring pastures crawling on their knees and not infrequently suffering from a cancerous affection of their rumps. . . . It deserves notice that the smelters are occasionally affected with cancerous disease in the scrotum, similar to that which infests chimney sweeps. . . ." (Haagensen). Inasmuch as these works have been closed for many decades, this source of occupational cancer has become extinguished. The observations made by Paris, therefore, have remained unconfirmed by later investigators.

After Paris' original communication, it was many years before occupational arsenical cancer was mentioned again in the medical literature. The majority of cases thus far reported from Europe were observed in England. In 1913 Nutt, Beattie and Pye-Smith, reviewing the literature, found only two cases, both occurring in English workers; one individual had carried tins of arsenic powder on his shoulder for a number of years and developed a cancer of the neck below the external ear; the second cancer was present in a man working in a sheep-dip factory (Eve, F. S., 1913, and Porter, C. R., 1913). The report of the Medical Chief Inspector of England and Wales, which had noted in 1902 the presence of respiratory symptoms, melanosis and hyperkeratoses of the skin among 20 men employed in making sheep-dip, mentioned in 1923 that three of these workers had developed, during the intervening years, epitheliomas of the skin. Four additional cases of arsenical cancer came to observation during the period covered by this report. One of these tumors occurred in a dye worker (Brezina). There were four fatalities among the seven cases recorded. When O'Donovan reported three new cases of arsenical malignancy of the skin in 1924, present in workers of English sheep-dip plants, he mentioned that Legge had seen three additional cases among the same class of workers. The annual report of the chief inspector for the year 1930 listed a new case found in a man engaged in the manufacture of emerald green (aceto-arsenite of copper). Henry, who examined 14 men with an

occupational exposure to a powder of arsenic and alkali, found in four of these workers ulcerations of the upper and lower limbs. These may have been chemical burns or may have represented ulcerated arsenical epitheliomas. There were in England, during the last five decades, a total of seventeen arsenical cancers of the skin, of which four must be regarded as doubtful.

During the same period continental Europe furnished two cases having this same etiology. A somewhat doubtful case was recorded by Ketron from France in 1928. The report stated that a cutaneous malignancy was observed in a machinist employed in a factory making buttons from brass containing 0.0074 per cent of arsenic. The development of the cancer was attributed to the inhalation of the brass dust. Germany contributed one case in 1938, when von Pein noted the occurrence of a malignant transformation of an arsenical keratosis in a vineyard worker, who had used an arsenical spray. A single case of arsenical carcinoma, present in an employee of an arsenic factory attached to a smelter of copper ores, was reported from Japan (Miyaji, 1935).

The occurrence of arsenical cancer of industrial genesis was reported from two American countries, namely, Mexico and the United States. Two cases of this disease were published by Anderson (1932) and Schaerrer (1934), respectively, in Mexicans. In both instances the tumors were seen in workers engaged in silver mining or smelting of silver ores. Anderson noted that, according to a statement made by his patient, similar cutaneous lesions are common among those members of the Mexican mining community who worked in the mines. By far the largest number of cases of arsenical malignancy has been reported during the last decade by investigators from the United States. Franseen and Taylor recorded two cases of cutaneous cancer in farmers, who had used arsenical sprays (1934). In the same year a report of Ayres and Anderson mentioned that there were ten cases of occupational arsenical epithelioma (3 after the use of arsenical sprays and 7 due to an exposure to fumes from smelters) among a total number of 41 cases of arsenical malignancy of known etiology. In spite of the fact that Australia is one of the principal arsenic producing countries, there are thus far no cases of industrial arsenical cancer placed on record from that continent. Altogether 34 cases of this disease were found in the literature, which is indeed an astonishingly small number, considering the conditions of exposure prevailing in certain occupations and the number of individuals exposed.

The impression prevailed even up to very recent times among some public health officials of this country that chronic arsenico-dermia of industrial origin did not exist in the United States. Schwartz stated in 1936 that he had not seen a single case of occupational arsenical keratosis or epithelioma among the arsenic workers he had examined. To explain this extraordinary immunity of American workers to arsenical malignancy, Schwartz advanced the opinion that either the American industries were newer than those of Europe and hence had more safety precautions installed in handling arsenic, or the methods

of handling arsenicals in Europe were perhaps cruder than those used in the United States, or the statistics gathered from Europe were from an earlier period, where cruder methods were employed and therefore more chronic poisonings occurred.

The actual evidence available, however, presents, a picture quite different from that painted by Schwartz. The United States has furnished not only the largest number of frank industrial arsenical cancers during the last ten years, but seems to lead all other countries in the number of chronic arsenical dermatoses of occupational origin, according to the data recorded in the literature. This fact is also in agreement with the conditions prevailing in this country in regard to the general handling of arsenicals. It is scarcely possible to take less precautionary measures and to handle arsenicals with more utter disregard of the general health than that which has been practised in our country in recent years (Jackson; Serles). Anyone who has watched the dusters and sprayers of arsenical insecticides at work, must have been impressed by the almost supreme carelessness with which these poisonous substances are dispensed.

Chronic arsenicism of industrial as well as non-industrial origin is evidently a disease which often is not recognized, but is diagnosed as some other disease producing similar symptoms. Hopkins and Van Studdiford remarked that an increased "arsenic consciousness" among physicians may show the more frequent relationship between cutaneous epitheliomas and arsenic exposure than heretofore. A similar opinion was expressed by Schöndorf, who noted that the symptomatology of chronic arsenicism apparently was not sufficiently well known among physicians and that, therefore, the occurrence of this disease and of its neoplastic sequelae was not properly appreciated. Leibowitz stated that arsenic intoxications frequently are not recognized during life because of the similarity of their symptoms with other diseases. In a discussion of medico-legal cases of arsenic poisoning, Marx expressed the view that arsenic poisoning is extraordinarily frequent, but often not recognized. Marx felt that the reasons for this failure were to be found in the difficulty of diagnosing arsenic poisoning from the symptoms presented clinically as well as at necropsy.

Franseen and Taylor emphasized that the carcinogenic properties of inorganic arsenic were not universally appreciated. A striking illustration of the importance of this fact was furnished recently by Ayres and Anderson. These investigators studied the palms and soles of every patient having a basal cell carcinoma, for the presence of hyperkeratoses, one of the most significant characteristics of chronic arsenico-dermia. In 75 per cent of 44 cases, discreet punctiform keratoses were found; in 12 out of 19 samples of urine examined, the presence of arsenic was demonstrated. The following observation reported by Montgomery a few years ago points in the same direction. This investigator demonstrated arsenic in the skin of a group of young individuals suffering from multiple basal cell carcinoma of the skin. There was no evidence of a

previous occupational or medical exposure to arsenic. Inasmuch as industrial arsenical dermatoses are not notifiable occupational diseases in many states of the United States, any reliable information concerning the incidence of this disorder among American workmen is non-existent.

The apparent and sometimes alleged harmlessness of the industrial exposure to arsenicals in regard to the genesis of cutaneous malignancy is also not borne out by the incidence of medicinal and environmental arsenical neoplasia of the skin, which is caused in many instances by arsenic compounds identical with those found in industrial activities. In spite of the fact that the medicinal and general environmental exposure to arsenic, resulting in cutaneous tumors, is in general less severe and less prolonged than that prevailing under many occupational conditions, the absolute number of medicinal arsenical malignancies reported is considerably higher than the figures available from industrial sources.

The medicinal origin of arsenical epitheliomas was described first by Hutchison in 1887, who had observed at that time several cases of this disease in persons with psoriasis treated with arsenicals. This observation has been confirmed many times (Ullmann; Crocker and Pernet; Darier; Lane; Simons; Dubreuilh; Darier; Lane; Hartzell; Bland-Sutton; Schamberg; Nutt, Beattie and Pye-Smith; Semon and Aliferis; White; Montgomery; Pye-Smith; MacCormac; Barber; Fassrainer; Milch; MacKee and Fordyce; Hamilton; Fonss; McNeer; Franseen and Taylor; Haagensen; Anderson; Hopkins and Van Studdiford; and others). The total number of medicinal cases of arsenical epithelioma is approximately 115, of which, however, a few cases may have been counted twice. There were mentioned an additional 90 cases of arsenical keratoses by the authors above listed.

The causal agents of medicinal, arsenical cancer were principally trivalent arsenic compounds, such as potassium arsenite contained in Fowler's solution (KOAsO) taken in the treatment of psoriasis, asthma, leukemia, anemia, migraine, epilepsy, acne, eczema, psychoneurosis, and syphilis or as a general tonic. In several cases arsenic was introduced medicinally with Donovan's solution (AsI_3 plus HgI_2) or with Asiatic pills (20 parts of As_2O_3 plus 80 parts of black pepper). The occurrence of arsenical epithelioma after the therapeutic introduction of organic arsenicals (arsphenamines, cacodylates) was observed less frequently (Ullmann; Cannon; Milch; Levin, Ayres and Anderson). There cannot remain any doubt as to the carcinogenic potentiality of these organic arsenicals, as arsenical keratoderma following the injection of these preparations has been reported repeatedly (Gauvain; McCleod; Timberlake; Ebert; Klauder; Philip; Heller; Hofmann).

Additional confirmation of the carcinogenic action of arsenic upon the epidermis is supplied by the observations regarding the occurrence of keratoderma and epithelioma in individuals who had a purely environmental exposure to arsenic due to contamination of the atmosphere or the drinking

water. The classical, but apparently not unique example of an endemic environmental contact with arsenic (present in the drinking water) is presented by the Reichenstein disease, which was observed among the inhabitants of the city of Reichenstein in Silesia.

The district of Reichenstein has been for the last 900 years the site of intensive mining activities (gold and silver ores and since 1698 also arsenic ores). During these centuries large spoil banks containing arsenic wastes accumulated in the neighborhood of the mine shafts. As the spring water coming from the nearby mountains ran through this area, arsenic was dissolved in it. Similarly, the underground water, from which most of the drinking water supply was obtained formerly, contained considerable amounts of arsenic (10 to 15 mgm. per liter, or about 10 times the minimal toxic dose). The arsenic content of this underground water was especially high wherever connections between the underground water and the water in the mine pits existed. In addition to this environmental exposure from the consumption of arsenic containing drinking water, there also existed an occupational type of contact for individuals employed in the construction trades, as the arsenic spoils in this region were used for building material and the preparation of mortar. Chronic arsenicism with its neuritic, gastro-intestinal, hepatic and cutaneous manifestations was a disease commonly observed among the inhabitants of Reichenstein for many centuries up to rather recent times. The first description of this important and interesting public health problem was rendered by Geyer in 1898, who mentioned that a high incidence of malignant tumors was observed among the inhabitants of this region. Geyer noted especially the occurrence of arsenical keratoses and epitheliomas. This observation was confirmed by several local physicians (Habel; Jahn; Wilde). A comprehensive report on the Reichenstein disease was published in 1937 by Kathe, in which the various aspects of this disorder were discussed in detail. Since the town was provided with a new and adequate water supply in 1928, through which the arsenic content of the water was lowered to a maximum of 0.015 mgm. per liter, it must be expected that this interesting source of endemic arsenicism will gradually lose most of its practical importance and will become a matter of past history (Gottron).

Recent reports from Argentina indicate that similar conditions as those observed in the Reichenstein district seem to exist in certain parts of Argentina. The drinking water in these parts contains appreciable amounts of arsenic and the occurrence of arsenical keratoses and epitheliomas among the inhabitants has been observed (Seminario and Alvarado; Fernández; Corbella; García and Ruiz; Alvarez). In a recent communication from this country, Arguello stated that 39 out of 323 cases of skin cancer treated at his clinic were of environmental arsenic origin, coming from a region in which chronic poisoning was endemic on account of the high arsenic content of the drinking water and the foodstuffs raised there.

Apart from these natural environmental sources of arsenic exposure, giving rise to neoplastic growths of the skin, there have come into existence various important artificial conditions of an environmental contact with arsenicals for the general population in many countries (Zangger). Some of these artificial environmental contaminations have produced similar effects as the natural ones, while in others the possibility and potentiality of such an action must be considered as a great probability.

In the first report dealing with the occurrence of industrial arsenical epithelioma, Paris mentioned the development of cancerous ulcers in domestic animals (horses and cows) grazing in meadows situated close to the copper smelters and tin-burning establishments. The arsenical fumes released from these plants into the atmosphere were precipitated upon the vegetation of the adjacent countryside. The arsenic contaminating the grass of the meadows was ingested by grazing animals and thus caused the development of the cancerous lesions. It was not until quite recent years that similar observations were made again. Wirth noted in 1922 that animals grazing near smelters showed signs of chronic arsenic poisoning. Prell reported in 1936 the occurrence of extensive arsenical injuries among the domestic and wild animal life in the region of Freiberg, Saxony, where numerous smelters (silver and lead) released arsenic containing fumes into the air. It was shown that these arsenical fumes were spread over an area measuring 50 km. in diameter and settled upon the vegetation. Horses, cows, goats, and pigs, feeding on this vegetable matter, developed loss of hair and hyperkeratoses, while melanotic spots and precancerous warts were seen occasionally on the skin of deer inhabiting the forests of this region. A carcinomatous lesion was found in one deer. In addition to the cutaneous manifestations of chronic arsenic poisoning, domestic, as well as wild animals, were affected by arsenical enteritis, gastric ulcers and cirrhosis of the liver. There existed in this area an extraordinary mortality among insects, especially bees. After rainfalls which washed the arsenical dust from the leaves and carried it along into the water of brooks and pools, a great many fish died, such as was also reported recently from France following the use of arsenical insecticides. Baader stated that somewhat similar conditions existed in other mining and industrial regions in Germany (Harz district, Rhineland).

Recently, Nieberle reported the endemic occurrence of adenocarcinoma of the nasal sinuses in a flock of sheep kept in the fume and dust zone of these smelters in Freiberg. He suggested that this condition was caused by the chronic introduction of arsenic, as not only was arsenic found in the brain, tumor tissue and liver of the affected animals, but attacks of acute arsenic poisoning with gastrointestinal manifestations were not uncommon among the sheep which furnished the cancerous animals. Commenting upon these findings, Baader suggested that in all probability not only the animals, but also the human inhabitants of such areas, were exposed to the arsenical environ-

mental hazard with its various organic effects, including carcinogenic sequelae. Baader added that these observations demonstrated that relatively small amounts of arsenic are evidently capable of producing severe organic damage in animal life.

It cannot be assumed that such deplorable pollutions of the atmosphere by arsenical fumes emitted by smelting establishments are confined to Germany. Prell stated, for instance, that the smelters of the Anaconda copper mines in Montana are said to release every day 26 tons of arsenic into the atmosphere. There are a great number of other industrial establishments in this and other countries which pollute the atmosphere with arsenical waste products to the detriment of the health of human and animal life inhabiting the environmental fume zone (Sowden).

While these sources of artificial environmental contamination with arsenical compounds are of more or less localized nature, as they depend upon the presence of certain mining and smelting activities of arsenic containing ores or of chemical industries handling larger amounts of arsenicals, the rapidly extending use of arsenical parasiticides and insecticides in agriculture and forestry has introduced a much more generalized health hazard. The quantities of arsenicals annually used in the United States for this purpose was estimated by Sturmer to have amounted to 80,000,000 pounds (mainly lead arsenate). It is likely that this figure is too low, as it was stated in an editorial appearing in the *Journal of the American Medical Association* in 1937, that one particular valley in the Pacific northwest received as much as 7,000,000 pounds of lead arsenate annually for the past twenty years. This means that approximately 50,000 tons of lead arsenate have permanently contaminated the soil of this valley and that a good portion of this arsenate is gradually taken up from the soil by vegetation growing in this valley. A part of the arsenical dusted or sprayed on fields, meadows, truck gardens, vineyards, orchards, lawns, fields and swamps remains attached to the leaves and fruits and represents a serious danger to those who ingest them. It has been reported that live stock was poisoned by the spray residue carried as "drift" to pastures from orchards that had been sprayed from airplanes. Similar observations were made in regard to man poisoned by the ingestion of fruits and vegetables sprayed with arsenicals (wine grapes, lettuce, spinach, beans, cabbage, and asparagus) (Evans; Medical News; Dörle and Ziegler; Ledoux; Tropp and Rauch; Mühlens; Thorel and Vinzent; Lendrich; and others). In instances several hundred individuals were poisoned acutely at one time by the ingestion of foodstuffs, usually wine, contaminated with arsenic, and developed later melanodermia and hyperkeratoses. Even the smoking of tobacco contaminated with arsenic has been the cause of arsenic poisoning in several cases (Barksdale).

Attention may be called to the fact, also, that the use of arsenical insecticides has given rise to an increase of the arsenic content in smaller and larger bodies of water. Such contamination may not only be injurious to the animal life

inhabiting such waters and to the human population using them for their supply of drinking water, but arsenic may be resorbed through the skin of persons bathing in such waters (Leva; Keeser).

Because of the frequent contact of the general population with arsenicals (contained in vegetables, fruits, drinking water, tobacco, wine, as the result of the use of arsenical sprays; in medicinal and cosmetic preparations used for therapeutic or prophylactic purposes; and as contaminants in materials employed in the preparation of foodstuffs [sugar, baking soda, syrup, and glycerin]) the occurrence of arsenic in the hairs, nails and urine of apparently normal persons has become a condition which is not unusual (Schwarz and Deckert; Oppenheim; Throne and Myers; Boos and Werby; Myers, Throne, Gustafson and Kingsbury; Holmes and Remington; Kunkel; White; Remington; Fordyce; Rosen and Myers; Gautier and Clausmann; Gautier; Ziemke; Brooke and Roberts; Barendt; and others). In a discussion of their observations Schwarz and Deckert contended that the demonstration of small amounts of arsenic in the hair is not indicative of arsenic poisoning. This statement is misleading, as the absolute amount of arsenic stored in these keratinous products of the skin is not a reliable index of the injurious action exerted by the arsenic in a particular individual, especially in subchronic poisoning in which definite clinical manifestations of arsenicism may be absent for many years. Occupational as well as general environmental conditions of exposure to arsenicals represent an actual health hazard to larger portions of the general population and have become a serious problem of public health (Myers).

IV. SYMPTOMATOLOGY

As arsenic is a capillary and metabolic poison, it affects many organs (nervous system, alimentary system, respiratory system, hematopoietic system) among which the skin is only one. Inasmuch as the cutaneous manifestations of chronic arsenicism, often accompanying the epitheliomatous lesions, are not always of such a character as to permit a definite diagnosis of their arsenical causation, and in view of the fact that a positive history of a previous occupational, medicinal or environmental exposure to this chemical cannot be obtained in an appreciable number of suspicious cases, a diligent search for additional signs and symptoms of arsenicism, including even transient ones of a rather remote past, must be made whenever indicated. It is essential to know, on the other hand, that cutaneous malignancy of arsenical genesis may represent sometimes the only apparent manifestation of chronic arsenicism. There may be a complete lack of any preceding symptoms of acute or chronic arsenic poisoning. The non-cutaneous manifestations of chronic arsenicism are as follows:

1) *Nervous system:* headache, dizziness, neuralgia, neuritis, paresis of motoric and sensory nerves, affecting especially extremities, paresthesias.

2) *Hematopoietic system:* anemia or, occasionally, polyglobulia.
3) *Alimentary system:* melanosis and leukoplakia of oral mucosa, gastro-enteritis, cirrhosis of the liver.
4) *Respiratory system:* ulceration and perforation of the nasal septum, pharyngitis, laryngitis, bronchitis.

The location and character of symptoms present in the individual case depend to a certain extent upon the type of contact. Mention may be made in this connection of the alleged occurrence of arsenical malignancies in organs other than the skin (carcinoma of the oral mucosa [Ullmann, K.]); carcinoma of the tongue (Kennaway); carcinoma of the esophagus (Franseen and Taylor); carcinoma of the stomach (Nutt, Beattie and Pye-Smith; Kennaway); carcinoma of the pancreas (Franseen and Taylor); carcinoma of the lung (Saupe).

The cutaneous manifestations observed with chronic arsenicism may develop in response to a direct contact of the skin with arsenic dust, fumes or vapors, resulting in a percutaneous resorption of the chemical. They may follow the introduction of arsenic by oral ingestion, inhalation or medicinal subcutaneous or intravenous injection of inorganic or organic arsenicals and their subsequent storage in and excretion by the various epithelial elements of the skin. The following non-cancerous, but in part, precancerous cutaneous lesions, may precede the development of or may accompany arsenical malignancy of the skin:

a) Disturbances in Pigmentation: one of the most constant and most characteristic symptoms are irregularities in the intensity and distribution of the melanin pigment indicating the presence of a generalized disturbance of the melanin metabolism. The skin assumes a greyish brown to deep brown color, which may approach black in extreme cases.

It is typical of arsenic melanosis that the pigmentation is not uniform in degree, but that areas with increased pigment content occur side by side with those showing a loss of melanin (leukoderma) (MacKee and Fordyce). In some cases the pigmentation exhibits the so-called "rain-drop" type of arrangement. A network-like distribution of the melanin sometimes may be recognized (Schöndorf). The melanosis is usually most pronounced in places which either normally show a high degree of pigmentation (buttocks, inguinal region, axillary region) or which are exposed to friction. The presence of capillary ectases in the face and of polyglobulism may give occasionally the affected individual a peculiar brownish red complexion. Arsenical melanosis in Negroes manifests itself by the appearance of black spots, like freckles, which gradually increase in size, number and distribution and which may alternate with more or less unpigmented areas. The arsenical melanosis resembles in appearance as well as in distribution (involvement of oral mucosa) the melanotic condition observed in Addison's disease. Melanosis is present in 50 per cent of arsenico-dermia with keratoses. The pigmentary changes may appear up to 30 years after the exposure to arsenicals (Montgomery).

b) Disturbances of Nail and Hair Growth: Diagonal white stripes, the so-called

Mees' stripes, become visible in the nails of fingers and toes 6 to 8 weeks after the introduction of toxic amounts of arsenic. They are the result of transient disturbances of the nail growth produced by the arsenic. The relative position of the stripes in the nails, determined by the average rate of nail growth, permits an estimation of the time at which a major arsenical exposure has taken place (Simons; Eichelbaum). It is obvious that these stripes are not demonstrable if the arsenical contact occurred years previously. Chronic arsenicism is accompanied sometimes by a spotty loss of hair (alopecia). It has also been noted that at the early stage of melanosis the hair follicles stand out as white points in a dark background, as they take up the pigment later than the rest of the skin.

c) Disturbances of the Epidermis Proper: The epidermal manifestations of chronic arsenicism are identical regardless of the type of introduction and the chemical character of the arsenical (Klauder; Brünauer; Andrews; Kyrle; and others). There exists, however, a great variability in the morphological appearance of these lesions, which may show, sometimes, a close resemblance with certain cutaneous disorders of non-arsenical etiology (psoriasis, herpes zoster). While the more or less acute cutaneous reactions to arsenic usually exhibit a vesico-pustulous eczema, the dermatoses observed as late manifestations of a chronic exposure are primarily more of a hypertrophic and atrophic nature, and display inflammatory changes mainly as the result of secondary complications.

Frequently a dry, seborrhoeic eczema exists associated with spotty pachydermia. Flat, discreet, reddish, well delimited, scaly keratotic areas with raised pearly borders as well as cutaneous horns may be found in restricted areas or diffusely distributed over the body. Lesions situated on the trunk start usually as rusty, scaling, crusty papules which gradually increase in diameter (up to 2 cm.) and become covered by hard crusts. These lesions occur in occupational arsenicism chiefly at sites exposed to arsenic dust (face, neck, chest, dorsum of hands, inguinal region). They are found, however, in contradistinction to similar changes of the senile and actinic origin, also in parts of the skin which are not exposed directly to the carcinogenic agent.

Common to the occupational as well as to the non-occupational arsenical exposure is the occurrence of marked hyperkeratotic areas with clavus-like elevations on the palms of the hands and on the soles of the feet. These keratotic lesions are rough and fissured and contain numerous small, hard, wart-like or stalactite-like horns. The hyperkeratoses of the palms and soles are said to originate usually from vesicles formed around the orifices of sweat-ducts which excrete an arsenic containing perspiration (Andrews; Brünauer). Not all hyperkeratotic formations exhibit progressive growth. Many may become stationary or may undergo involution after a cessation of exposure to arsenic (Montgomery). Some however, increase in size, become nodular, ulcerate and finally assume a malignant character.

The malignant lesions, which are often multiple (in 50 per cent of the arsenical malignancies of Pye-Smith; in 33 per cent of Arguello's cases [5 per cent multiplicity in skin cancer in general]) may exhibit the gross appearance

of different types of cutaneous epitheliomas. Many show the characteristics of ulcerating fungating cancroids; others resemble rodent ulcers (Montgomery; Franseen and Taylor; MacKee and Fordyce; Barber; MacCormac; Cannon; Ullmann, K.; and others). Recent investigations have shown that arsenical malignancies may imitate the appearance of certain intraepithelial epitheliomatoses (Bowen's disease) (Franseen and Taylor; Montgomery; Anderson) and of extramammary Paget's disease (Franseen and Taylor). Montgomery, as well as Anderson, recorded arsenical lesions resembling multiple superficial epitheliomatosis. It has been observed repeatedly that epithelial tumors of different types coexisted in the same individual (Andrews).

The ultimate malignant outcome of an arsenical dermatosis does not depend so much on the dose and duration of exposure to arsenic, as on a certain individual susceptibility and reactivity, which may be related possibly to the definitely allergic character of the chronic arsenico-dermia (Oppenheim; Schöndorf; and others).

V. SITE OF ARSENICAL EPITHELIOMAS

It has been stated by several investigators (Fassrainer; Montgomery) that non-occupational and occupational arsenical epitheliomas differ in their respective location. While the medicinal tumors affect mainly the palms, soles, fingers, toes and rarely the back of the hands, the industrial neoplasms involve more often the face, cheeks, eyelids, shoulders and neck and less frequently the region of the groin. These variations are attributed to the fact that in industrial arsenical cancer the local distribution follows in general the sites of most intense exposure to the cancerous agent. Arguello mentioned that 38 per cent of the arsenic cancer due to consumption of contaminated drinking water and foodstuffs were located on the extremities (in contrast to 4 per cent of this location among skin cancers in general). The next most frequent location in Arguello's series was the trunk, while the head was least often affected.

Table I may illustrate the distribution of 17 industrial cancers, of which three were of multicentric type, and of 117 non-occupational (mainly medicinal) epitheliomata, of which 18 were multiple.

VI. SEX AND AGE

The industrial arsenical cancers (13) occurred in males exclusively. Also the non-occupational epitheliomata were predominantly in males (the ratio of males to females was approximately 4:1).

It has been observed in accord with other occupational tumors and neoplasms of environmental origin that the age of onset of arsenic malignancy is in general in an earlier age group than that noted in the corresponding cryptogenetic type of cancer. Pye-Smith stated that 25 per cent of all arsenic cancers occur in individuals below the age of 35, and Ullmann mentioned that arsenic epithelioma appears usually before 40 years of age.

TABLE I. SITES OF ARSENIC EPITHELIOMATA

Site	Non-Occupational	Occupational
Scrotum	11	1
Vulva	4	0
Perineum	5	1
Head, Neck, Face	13	5
Eyelids	1	1
Shoulder, Arm, Wrist	14	2
Fingers, Hand	30	1
Leg	9	1
Foot, Toes	11	1
Trunk	19	4
Total	117*	17

* In the preparation of this compilation the data given by Kennaway were included. It is, therefore, likely that a certain amount of duplication is present in this column.

Table II shows the age distribution for the industrial and non-occupational arsenic cancers, respectively, arranged in decades.

TABLE II. AGE DISTRIBUTION

Age	1–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80
Occupational				4	3	5	1	
Medicinal	1		3	6	7	5	3	1

The shift toward the younger age groups is evident from Table II, as 24 of the 39 tumors were found in individuals less than 50 years of age. The average age at the appearance of precancerous keratoses is 41 years (range 11-74 years), according to Montgomery.

VII. TIME OF EXPOSURE

The data available regarding the time of exposure are incomplete and not very reliable, particularily concerning the medicinal cases, as here the exposure to arsenic containing medication was often an irregular and rather remote one. Table III is presented, therefore, with a certain amount of reservation.

TABLE III. TIME OF EXPOSURE

Years	1–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40
Industrial	1			5	2	3	2	2
Medicinal	5	3	2		1		1	

Table III exhibits a striking difference in the duration of exposure to arsenicals existing between the occupational and non-occupational cases. This relation is an actual one, inasmuch as clinical observations agree on the fact that arsenical cancer may follow upon a rather brief medicinal exposure to arsenic.

Interval Between Time of Exposure and Appearance of Neoplasm. From a few to many years may elapse between the last contact with arsenic and the appearance of a neoplastic reaction (MacCleod; McNeer). The range is from 2 to 60 years. The following tabulation (Table IV) of 13 medicinal cases may give an approximate idea of these relations.

TABLE IV. INTERVAL BETWEEN EXPOSURE AND NEOPLASTIC REACTION

Years	1–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	60
Cases	1	1	7	1	2	1		1		1

VIII. BIOLOGICAL BEHAVIOR

Arsenic epitheliomata usually are slowly growing tumors, which produce only late metastases in the regionary lymph nodes. Two-thirds of the cases, however, produce ultimately metastases (Franseen and Taylor). In spite of this relatively mild aggressiveness, the ultimate prognosis of arsenical malignancy is not considered to be favorable, as the disease manifestations are not infrequently multicentric and an effective permanent local control of the cutaneous disorder is for this reason difficult or impossible (Ullmann; Bland-Sutton; Franseen and Taylor; Mason; von Pein; Bering and Zitzke).

IX. PATHOLOGY

The hyperkeratotic, warty formations are covered by a thickened, lamellated cornified layer, which extends into the sweat gland ducts and which does not contain any nuclei. There are, however, oval to round spaces, some of which are filled with an eleidin network. The stratum lucidum is usually distinct. The granular layer is thickened. The upper rows of epithelial cells of this stratum contain kerato-hyaline granules, which are dark stained by hematoxylin. In acanthotic, flat warts the kerato-hyaline granules are scanty. Toward the center of these warts the granular cells are less closely packed, irregularly shaped, partly spindle shaped and contain faintly stained nuclei. The deeper layer of granular cells and spinous cells is composed often of degenerated cells with perinuclear vacuoles or consists of accumulations of kerato-hyaline granules or of vacuolated, anuclear cells. There occur epithelial giant cells and amitotic divisions. The degenerative changes may extend into the basal layer, whose cells contain a dark brown pigment. The rete pegs are elongated. In the under-

lying connective tissue, there is often an increase of the fixed phagocytic cells. Inflammatory lymphocytic reactions are of secondary nature. During the early dyskeratotic phase of the epidermis, there are no pathological changes in the papillary body and cutis. An increase in the vascularity develops later in the papillae. The small arterioles proliferate and become dilated. The capillaries may show a mild perithelial thickening and minor pigmentary deposits may appear alongside the vessels. There are no changes in the sweat glands. The center of the high cutaneous horns is occupied by parakeratotic masses composed of lamellae with onion-like arrangement. Cellular acanthosis may be found in all epidermal layers. The basal cells show in places numerous mitoses and contain vacuoles. The rete pegs are pointed, broad or club-shaped. There exists a rarefaction and granular disintegration of the elastic fibrils in the interpapillary region. In lesions that show still more advanced epithelial changes, the epidermis may exhibit the morphological characteristics of a malignant dyskeratosis similar to that seen in Bowen's disease. With increasing loss of polarity and ensuing infiltrative growth of the epithelial cells, the lesions assume the character of a squamous cell carcinoma. In some instances, on the other hand, the epidermis undergoes alterations which correspond with the various developmental phases of basal cell cancers.

The majority of the arsenical epitheliomas are histologically cornified squamous cell carcinomas. They belong in general to the low and moderate grades of malignancy. In a series of 23 arsenical cancers studied by Franseen and Taylor, 9 were epidermoid carcinomas of Grade I, 4 were epidermoid carcinomas of Grade II, 1 was a mixed baso-epidermoid cancer, and 9 were basal cell cancers. Montgomery stated that the arsenical epitheliomata of epidermoid type, while belonging usually in the histological malignancy Grades II and III, ran usually a less malignant course than the ordinary epidermoid carcinomas of the same grades. A reliable prognostication of arsenical cancers on the basis of their histological structure is considered therefore not feasible by Montgomery.

X. HISTO-CHEMISTRY

The skin and its appendiceal organs (sweat glands, sebaceous glands, milk glands, hair follicles, nail beds) belong to those organs in which arsenic is deposited chiefly after chronic exposure and through which this chemical is excreted to an appreciable degree. The arsenic is contained in the horny scales, the sweat, the sebum, the hairs, the nails and in the milk (Schlossberger). The special affinity of the skin for arsenic and thereby the accumulation of this substance in the skin depends upon the large amount of sulfhydryl compounds which are present in the cells and products of this organ, as sulfur compounds are used for the manufacture of keratin, hairs and nails. Histochemical methods have been developed for the histochemical demonstration and localization of these arsenical deposits in the various component parts of the skin. The dif-

ferent techniques proposed for this purpose are based upon the formation of arsenic trisulfide (As_2S_3) which is obtained in the form of yellow-brown to greenish yellow, rounded and elongated, highly refractive crystals, which are insoluble in water, alcohol, xylol and Canada balsam, but soluble in ammonium carbonate, potassium hydroxide and ammonium hydroxide. The fundamental aspects of these methods were developed by Justus in 1905. Modifications and improvements were developed later by Osborne and Brünauer. According to recent investigations of Tannenholz and Muir, this method is not entirely specific for arsenic trisulfide, as similar crystals may be formed, apparently representing a combination of sulphur-proteins.

Osborne's Method:

1) Tissue is fixed in a 10 per cent formalin solution for 24 to 48 hours.
2) It is then washed in running tap water for at least 6 hours, better for 24 hours.
3) The tissue is then cut into small and thin slices, not more than 2 mm. thick.
4) The slices are placed into a one ounce glass stoppered bottle filled with a freshly prepared, neutral hydrogen sulfide solution. A small amount of liquid petrolatum is put on the stopper, which is then tightly inserted, and bound down by a cord. The bottle is placed into an incubator at 70°C for 4 days. Fresh hydrogen sulfide is added every day. If the slices are placed into a pyrex tube which is sealed in an oxygen flame, this procedure is not necessary. As the stainability of the tissue is greatly reduced, if they are kept at a temperature of 70°C, the container may be kept in an incubator of 56°C for 6 days instead. The surface of the tissue assumes a dirty grey to black color on account of the formation and precipitation of iron sulfide.
5) The tissue is then washed again in running water for 6 to 12 hours.
6) Dehydration is accomplished in successive steps in a 50 per cent to 100 per cent alcohol series containing an addition of 10 per cent ether.
7) It is then embedded in celloidin and sections five microns thick are prepared.
8) The cut sections are placed for 20 minutes into a 10 per cent HCl solution in 70 per cent alcohol. This procedure is essential, since all sulphides precipitated by the hydrogen sulfide in the tissues are dissolved with the exception of the insoluble arsenic trisulfide. This procedure impairs, however, the stainability of the sections.
9) The sections are washed in 70 per cent alcohol for 20 minutes and then stained with hematoxylin and eosin.
10) They are differentiated in 95 per cent alcohol.
11) The sections are cleared in oil-of-clove; the excess is removed with xylol.
12) They are finally mounted in Canada balsam.

The irregularly round to oval, bright yellow crystals of arsenic trisulfide, varying in size from 0.0005 to 0.00075 mm. in diameter have a faintly greenish tint. When they are viewed well focused under the microscope, they appear as solid crystals with a bright halo. The high refractivity and the greenish halo of the arsenic trisulfide crystals distinguishes them from similarly colored granules of non-arsenical nature (melanin-lipoid pigment, particles

of fat, various exogenous matter) which may be present in the tissue. The arsenic crystals are evenly distributed between the cells of the cornified layer of keratoses as well as of the normal skin. It is uncertain, whether any of these crystals are ever located within the cells. A great deal of arsenic is found in the granular, spinous and basal layers. Especially dense accumulations of yellow crystals often occur in the neighborhood of the intra-epidermal degenerative and necrotic foci. The largest amounts of arsenic can be demonstrated in the basal layer and in the papillary portion of the corium, especially in places located directly beneath intra-epithelial necroses. The corium is in general relatively free from arsenic. Minor quantities of arsenic may occur in the sweat ducts and in the walls and lumina of the sweat glands. The largest deposits of arsenic are found in areas showing the greatest vascularity. The bulk of the arsenic present in the epidermis proper is passed extracellularly to the outside. Considerable quantities of arsenic can be visualized in the sebaceous glands, the hair follicles, hair sheaths and hair shafts.

Trivalent arsenic contained in aromatic compounds exhibits, according to Osborne, a special affinity to the vascular structures of the skin, such as the small arterioles and capillaries beneath the papillae. The same investigator contended that different cellular elements participate in the excretion of arsenic depending upon its various valencies. Inasmuch as Osborne considered in this connection the arsenic present in arsphenamine as pentavalent, while, in fact, it is trivalent, this contention must be reexamined and confirmed before it can be accepted as correct.

Arsenic, once deposited in the skin, may be retained there for many years, according to Osborne. This statement is in general agreement with the observation made by various investigators indicating that the arsenic content of so-called normal skin increases with age. It is important to mention in this connection that arsenic may be demonstrated by the histochemical method of Osborne in pathological amounts in the skin of individuals which show neither keratoses, melanosis nor malignant lesions, and that, on the other hand, no arsenic may be demonstrable in the epidermis of individuals who had an established exposure to arsenic. The quantitative analysis of an arsenical epithelioma made by Osborne showed an arsenic content of 0.086 mgm. per gram of tumor tissue.

The diagnosis of an arsenical epithelioma of the skin depends upon the presence of the following evidence: (*a*) a positive history of exposure to arsenic; (*b*) clinical demonstration of cutaneous manifestations characteristic of arsenico-dermia; (*c*) histochemical demonstration of arsenic in the skin; (*d*) demonstration of arsenic in hair and urine; (*e*) diminution of the arsenic content in the urine with clinical improvement brought about by treatment with sodium thiosulfate; (*f*) exacerbation of symptoms upon renewed contact with arsenic; (*g*) positive patch test with arsenic (allergy) (Ayres and Anderson).

XI. EXPERIMENTAL ARSENICAL CANCER

The experimental production of arsenical cancers in the skin of animals has been attempted repeatedly, but has been accomplished only in a few isolated cases. Maisin, for instance, reported his failure to elicit cancerous reactions in the skin of mice treated with arsenicals. The oral introduction of potassium arsenite into rats and mice was tried unsuccessfully by Leitch. In a second experimental series, consisting of 100 mice which received cutaneous applications of an alcoholic solution of potassium arsenite (0.12 per cent) three times weekly, only one mouse developed, after 88 days of medication, a wart which ultimately became malignant (squamous cell carcinoma). The result obtained is not convincing, not only because of the singularity of tumor production in this series, but also in view of the fact that Leitch was unable to produce any tumors in a second series of mice similarly treated. Leitch felt that the high mortality prevailing among the treated mice accounted in part for this failure.

The experiments of Raposo were apparently more successful and conclusive. This investigator applied a mixture of vaselin and arsenic anhydride (100:10) to the ears of 10 rabbits. In five rabbits this mixture was heated to a temperature of 55°C before application, while the remaining five animals received it at normal room temperature. After 70 days of this treatment, there were hyperkeratoses and hyperplasias on the ears of 3 rabbits in each of the two groups, whereas papillomas were found in two rabbits treated with the cold ointment and in one rabbit exposed to the heated ointment. A cancroid was present at that time in one of the rabbits receiving the applications with the heated vaselin-arsenic mixture. Somewhat similar results were reported by Cholewa, who administered subcutaneously to two rabbits daily 1 cc. of a 1 per cent solution of potassium arsenite for a period of 6 months. After one year papillomatous warts appeared on the ear of the one rabbit which survived for this length of time. There existed a sarcoma of the perichondrium of the ear, located beneath the warty area.

Inasmuch as some investigators contend that the carcinogenic action exerted by arsenic is mainly an indirect one by producing certain changes in the cellular metabolism which create a local or general predisposition for the direct blastogenic influence of other agents (Fischer-Wasels; Büngeler), attempts were made to demonstrate experimentally this alleged effect of arsenic. Choldin injected mice for this purpose with arsenious acid preparatory to a series of cutaneous application of tar. Tar tumors developed somewhat earlier in these mice, than in a control series treated with tar only. Ciechanowski reported that the appearance of papillary and other precancerous lesions in the skin of tarred rabbits could be accelerated by the administration of arsenic. While these results seem to suggest that arsenic may exert a hastening influence upon the development of tar neoplasms in mice, Raposo's experiments conducted with rabbits fed arsenic and painted with tar were inconclusive in this respect. Contradictory observations were recorded concerning the proliferation stimulating

action of arsenic upon well established cancers. Sticker, Möller, Bierich, Schiller, Funk, and Rosen noted that the introduction of arsenic into tumor bearing animals exterted either no effect or a transitory inhibitory one upon their proliferative activity. On the other hand, Califano, Rocmans, and Hueper and Itami reported a stimulating effect upon the tumor growth following the administration of arsenicals. While Minot recorded that arsenic is not stored especially in tumor tissue, Hueper and Itami demonstrated appreciable quantities of this substance in spontaneous mammary carcinomas of mice subjected to repeated intravenous injections of neoarsphenamine. It appears possible that some of the contradictory observations made may be attributable to the fact that arsenic shows an affinity to certain tissues, in which it is stored or through which it is excreted, and may exert a stimulating effect upon neoplasms originating from such tissues, while being ineffective in those of different histogenesis.

Another approach for demonstrating the carcinogenic action of arsenic, which was based on the Cohnheim's theory, was chosen by Askanazy. This investigator transplanted rat embryos into the peritoneal cavity of adult rats receiving Fowler's solution in their drinking water. Benign and malignant teratomatous neoplasms developed in some of these animals. Adeno-myosarcomas were obtained by Maisin and Dupuis in two out of 26 rats injected with embryo pulp and Fowler's solution. This experiment was repeated in a somewhat modified form by McJunkin and Cikrit, who injected rat embryo pulp treated with arsenious acid into the testes, uterine horns and thighs of rats. A cystadenoma and a teratoma were the only tumors seen, appearing in the thighs of two rats. As similar teratomatous products were obtained in rats injected with embryo pulp only, the blastogenic rôle of the arsenic in this experiment remained undetermined. Carrell injected chick embryo pulp together with arsenious acid solution into fowls and obtained sarcomas. While White could confirm these results, Begg and Cramer, Leitch, Kauffmann, and Collier and Hartnack failed to do so.

An evaluation of the experimental data presented shows clearly that the experimental evidence concerning the carcinogenic properties and action-mechanism of arsenic is by far not as abundant and unequivocal as that available regarding other carcinogenic agents of similar occupational importance. Extensive additional experimental studies of arsenic as a carcinogenic agent are therefore urgently needed.

XII. CAUSATIVE MECHANISM

The causative mechanism operative in arsenical malignancy is still completely obscure. Various hypothetical explanations have been advanced, which are presented to reveal not only the various conceptions and to comment on their relative merits, but to demonstrate also the complexity of the conditions encountered in this respect.

In his discussion of the etiology of cancer, Eggers summarizes the rôle which arsenic apparently plays in this connection as follows: "Although many of the experimental studies of arsenic have indicated its ability to act as a local cancerogenic agent, its outstanding clinical significance appears to be as an agent that seems to cause a decided increase of predisposition to cancer, so that under its influence cancer may appear in humans at an unusually early age, and in sites that are commonly spared, but in which an added element of irritation that in ordinary conditions would be inadequate comes into operation." While no fault can be found with this statement, the controversial aspects enter into this problem with the various theories proposed as to the mechanism which brings about these effects.

Some investigators (Billeter and Marfurt; Dustin; and others) support the viewpoint that arsenic is an agent directly stimulating cellular proliferation and thus is primarily responsible for the ensuing cancerous growth. It is assumed that the cancerization of the epidermal cells occurs during the period of arsenical contact and that the delayed appearance of the neoplasms is caused by the fact that the cancerized cells remain quiescent for an extended length of time (Ullmann, K.). At the event of the cancerous manifestation, the offending agent is thought to have departed from the scene of action long before the end of the latency period (Barry, Bunbury and Kennaway). More recent observations seem to indicate, however, that this contention is not correct in a great number of cases, in which it was possible, to demonstrate by histochemical methods the presence of arsenic in the epidermis containing the malignant lesions.

The immediate cause of cellular cancerization is believed by some investigators to lie in the metabolic disturbances set up in the cells under the influence of arsenic. Osborne cited Bing and Schulz, Brooke and Roberts, and Wile, for the fact that arsenic may stimulate the oxidation-reduction rhythm of the cells to such a degree that the increased oxidation processes may carry the cells into a state of exhaustion and even death. This excessive chemical stimulation of the cellular metabolism is, in the opinion of Osborne, the cause of the ensuing dermatosis and its ultimate malignant transformation. While an adequate oxygenation is essential for a sustained cellular proliferation, there does not exist experimental or clinical evidence supporting the claim that an excessive oxygenation alone can be considered as the exclusive cause of a cancerous transformation of any type of cell.

A theory diametrically opposed to the metabolic aspects of the one just discussed was proposed by Fischer-Wasels and Büngeler. These investigators observed in the tissues of rats, to which arsenic had been administered in small doses over a long period, a distinct but slight reduction of oxidative activity, an increase of anaerobic glycolysis and the appearance of aerobic glycolysis. Fischer-Wasels and Büngeler concluded from this evidence that the interference of arsenic with the normal respiratory metabolism of the cells resulted

in a state favoring a cancerous transformation in analogy with the theory propounded by Warburg as to the causal significance of the fermentative processes in the cancerization of cells. It may be mentioned in this connection that Voegtlin and his coworkers maintained that arsenic is detoxified in the body by being coupled with sulfhydryl groups, a reaction which would impair the normal cellular oxidation-reduction mechanism.

A retarding action of arsenic upon three oxidation-reduction systems (hypoxanthine and xanthine oxidase; acetaldehyde, glycine and phosphate; acetaldehyde and colloidal platinum) was reported by Barry, Bunbury and Kennaway. These investigators stated, however, that no direct conclusions can be drawn from in vitro experiments upon biologic processes requiring months and years. Apart from the serious biological and technical objections which may be raised against the method used and the interpretations made by Fischer-Wasels and Büngeler, there remains the outstanding fact that the fermentation theory of carcinogenesis is entirely inadequate to furnish any intelligent explanation for the delayed appearance of the arsenical neoplasms.

This argument also militates strongly against the applicability of the Cohnheim's theory in connection with the causation of arsenical malignancy. In spite of the severe disturbances produced in the melanin metabolism by the influence of arsenic, there has not come to observation a single case of malignant melanoma of the skin originating from an activation of a pigmented or nonpigmented nevus. The alleged metabolic cancerigenic effect of arsenic is unable therefore to stimulate even congenitally misplaced and functionally disturbed embryonic cells into a malignant transformation. The character of the histological changes observed in the epidermis, as well as the site and the multiplicity of the arsenical neoplasms, eliminate the Cohnheim's theory from any serious consideration.

In view of the apparent stimulation of melanin production by arsenicals (Thorne and Myers), Stewart suggested that pigmentary disturbances set up by arsenic might be related to the carcinogenic action exerted by this chemical. A certain amount of support for this hypothesis may come from the fact that melanin contains cyclic hydrocarbons, and that melanosis is a feature common to various other precancerous cutaneous conditions, following upon an exposure to various occupational carcinogenic physical and chemical agents (pitch, tar, crude mineral oil, ultraviolet rays, roentgen-rays, radioactive substances). Ayres and Anderson have pointed out that arsenic seems to have photosensitizing properties, as arsenical eruptions appear first and most pronounced in areas exposed to sunlight, but the development of arsenical malignancy does not depend upon the actions of an actinic factor (Montgomery). The information available at the present time does not permit this hypothesis to be regarded except as an intriguing and interesting supposition.

An analysis of the various factors which may enter in the causation of arsenical neoplasia would be incomplete without mentioning the marked vari-

ability of the individual reactivity to arsenicals (Schöndorf; Thorne and Myers; and others). Thorne and Myers have suggested that the differences in sensitivity might be related to individual variations in the rate of elimination of arsenic, as they observed that some individuals excrete arsenic readily, while others retain it to varying degrees. These investigators observed, furthermore, that retention and elimination do not proceed at a constant rate in the same individual, but that these processes vary apparently with the acid-base equilibrium, so that there are periods of ebb and flow in these phenomena. Failure to excrete arsenic readily and properly may result, with chronic exposure, in a gradual accumulation of the chemical in the body and thus may cause appreciable differences in the actual degrees of exposure between several individuals receiving apparently the same dose of arsenic. It appears to be possible that such individual variations in the type and rate of detoxication and excretion may account for the differences in sensitivity observed. These observations and considerations are important because arsenic is an agent which gives rise to allergic cutaneous reactions (Reuter; Oppenheim; Ayres and Anderson; and others). Ayres and Anderson have pointed out that the erythematous and exfoliative arsenical eruptions may assume a fixed allergic character, as they flare up with each new contact and are followed occasionally by cutaneous atrophy.

If such a mechanism should play a rôle in the production of arsenic cancer, it must be assumed that arsenic combines as a hapten with protein molecules of the skin, thereby becoming an allergen, which in turn may cause a cutaneous sensitization. The in vitro experiments of Landsteiner have shown that aromatic arseno-compounds may be transformed into such allergens by coupling through diazotization with protein molecules (arseno-azoproteins). These arseno-proteins are chemo-allergens capable of causing the production of immune bodies and chemo-specific hypersensitivity (Marrack). Very stable compounds of arsenic with proteins can be produced also by the action of arsenic trichloride upon various proteins in connection with phosphorus pentoxide. The arsenic in these compounds is bound so firmly to the protein that it does not respond to the ordinary qualitative tests for arsenic (Raiziss and Gavron). Consideration also may be given to the fact that arsenic may couple with natural phosphatides dissolved in organic solvents, producing compounds which are soluble in ether, fats and oils. The available data suggest the possibility that an allergic component may be active in the pathogenesis of arsenical dermatoses and their neoplastic sequelae. Non-specific inflammatory reactions do not seem to play, on the other hand, any important part in the production of these tumors, as intra-epithelial alterations usually precede the onset of inflammatory changes in the cutis. Their rôle is an adjuvant one, as inflammatory processes may accentuate the permeability of the epidermis to arsenic and may aid possibly in the fixation of an allergic reaction.

XIII. THERAPY

Therapeutic measures intended for individuals suffering from the neoplastic sequelae of chronic arsenicism or potentially endangered by them, must be directed against any further continuation of the toxic and specific action of the arsenic stored in the tissues and must hasten its elimination. Furthermore, they must eradicate any precancerous or cancerous lesions already formed (Schöndorf; Franseen and Taylor; Thorne and Myers; Leibowitz; and others). Sweat cures (hot baths) are indicated for stimulating the production of sweat and the excretion of arsenic thereby. The intestinal function must be regular and prompt to favor the elimination of arsenic through the bowel. In cases in which occupational activities or environmental conditions necessitate the continued contact with arsenic, siliceous earth may be given by mouth as an adsorbent to prevent the resorption of arsenic through the intestine. Enterically coated tablets of sodium thiosulfate (0.5 gm. daily) may be given to convert the arsenic stored in the tissue into a non-toxic, insoluble, inert arsenic sulfide and to stimulate at the same time the removal of arsenic from the body. Such elimination treatments may be given to occupationally endangered persons in intervals of approximately 6 months. Where indicated, these treatments may be supported by the intravenous injection of 0.5 to 1 gm. of sodium thiosulfate in a 10 per cent aqueous solution every third day. Sodium thiosulfate may be given orally during the intervening days. The sodium thiosulfate solution intended for intravenous use must be freshly prepared. This type of treatment has no effect upon the arsenic content of hyperkeratoses, as these are rather avascular. The sodium thiosulfate, therefore, does not reach these depots and thus cannot mobilize the arsenic in them. The indiscriminate introduction of sodium thiosulfate into the body may result in the production of an alkalosis. Control of the carbon dioxide combining power of the blood is therefore necessary when such therapeutic procedures are employed. A chloride content of the blood over 500 mgm. represents an absolute contraindication to sodium thiosulfate medication. Keratolytic ointments (salicylic acid, etc.) may be applied for the local removal of the keratin masses covering hyperkeratoses. The local eradication of precancerous and cancerous arsenical lesions requires the same technical procedures as employed in the treatment of neoplastic cutaneous processes in general (electro-coagulation, roentgen-rays, radium, surgical excision). A block excision of the lymph nodes in the tributary regions is indicated in the case of a squamous cell carcinoma, as two-thirds of these tumors produce metastases in the regionary nodes.

XIV. PREVENTIVE AND SANITARY MEASURES

a) Medical Measures: The following medical measures should be observed in arsenic operations. Workers engaged in the production and handling of arsenicals and exposed to arsenical dust, fumes and vapors should wear special dust-proof clothing fitting tight around the neck and ankles (leggings or

bicycle clamps at bottom of trousers), dust-tight spectacles, respirators covering mouth and nose, rubber or cotton gloves or leather mittens, and rubber boots. The exposed parts of the skin as well as the unexposed and tender portions (armpits, region of groins, scrotum) should be covered with a protective ointment. Workers should be advised of the necessity of using the greatest personal cleanliness, giving special attention to the haired parts, the scrotum, groins and axillary pits, as dust and fumes are apt to filter through beneath the clothes in spite of every precaution. The arsenical dust tends to cause a dermatitis in regions where the skin is easily macerated by the sweat. Milk should be consumed freely. Bowel movements should be regulated by laxatives, if normally insufficient. Individuals with liver diseases, gastro-intestinal disorders, especially marked constipation, defective renal function, and abnormal cutaneous sensitivity to arsenic should be excluded from any employment in arsenic plants. Thorough periodical medical examinations of the workers should be made in yearly intervals for the determination of signs of acute or chronic arsenicism. These examinations should include quantitative tests for arsenic in the feces, urine, hairs, and nails, to obtain information regarding the elimination and retention of arsenic in the individual workers and to exclude those, which show excessive amounts of arsenic in these products, from further contact with the offending agent. The same steps should be taken if evidence of liver injury and chronic hyperplastic arsenico-dermia is apparent. The diet should contain adequate quantities of sulfur-containing compounds used in the metabolic detoxication of arsenicals.

b) Technical Measures: The technical measures to be taken for reducing the arsenic hazard must be directed toward eliminating the production of dust and fumes. The air in workrooms should be kept humid. The walls and floors of plants should be washed at frequent intervals. The handling of arsenicals should be done, as far as possible, automatically in closed systems. Wherever the production of dust and fumes cannot be avoided, efficient exhaust ventilation systems should be installed. Locker rooms remote from workrooms and adequate facilities for hot showers should be provided for workers. No food should be permitted to be brought into workrooms. Workers should be obliged to wash hands and face, before eating their food in clean and sanitary rooms reserved for this purpose.

XV. PUBLIC HEALTH ASPECTS

The data presented cannot leave any doubt that the occupational as well as environmental exposure to arsenic represents a serious and almost universal health hazard in many civilized countries, deserving the earnest attention of all public health authorities and legislative bodies. Under the circumstances that prevail in most countries, it seems advisable to regulate by legislative measures the introduction and rigid enforcement of the necessary technical and medical procedures as well as the installation of adequate equipment to

insure the safe production and handling of arsenicals. The employment of women and children in arsenic factories should be forbidden. Laws should be passed to prohibit the release of arsenic-containing fumes from stacks of smelters and other industrial establishments into the atmosphere. Laws should provide for the obligatory installation of neutralization apparatus for the removal of arsenic from the waste gases of such plants.

The use of arsenic-containing dyes for objects employed in the household, as clothing, wall paper, and wall paint should be forbidden. Laws to this effect were passed in Germany (in 1879), and in Sweden and Norway, and similar restrictions are in force in the United States and France.

The recent investigations of Hanzlik, Myers and coworkers, and Calvery and associates, concerning the general health hazard introduced by the use of arsenicals as insecticides, have shown clearly that the chief danger is not represented by acute, accidental poisonings, but by the great opportunity created for the occurrence of insidious chronic poisonings, especially in their latent, metatoxic form. The actual existence of such a hazard in this country has been emphasized repeatedly in editorials published in the *Journal of the American Medical Association.* It becomes an urgent necessity and duty for every government to study carefully the existing laws covering the arsenic hazard and to determine whether these laws are adequate in protecting the health of workers engaged in operations with arsenicals as well as of the general population which is exposed to risk in the consumption of foodstuffs treated with arsenicals.

In the United States federal laws regulating the use and content of arsenicals in foodstuffs introduced as a contaminant by insecticide sprays, with chemicals used in the manufacture of foods, by factory processing equipment and other means, cover only products handled in interstate commerce (Farmer's Bulletin 1752, U. S. Department of Agriculture, 1935). They have no effect upon and exert no control over foodstuffs shipped and traded in intrastate commerce. In 1937 there were only two states in the United States (Colorado and Michigan) in which laws fixed the upper limit of the permissible arsenic content of foodstuffs and thus provided some protection to consumers of fruits and vegetables produced and distributed within the state.

The United States Department of Agriculture allows in foodstuffs 1.06 parts of arsenic (as As.) or 1.4 parts of arsenic (as As_2O_3) per million parts of food. Similar figures and regulations were set up by the British Royal Commission. The United States Department of Agriculture recommends the removal of the traces of arsenic by rinsing fruits with a dilute solution of hydrochloric acid. While this procedure is effective in a limited degree with most fruits, it is inadequate for leafy vegetables, cauliflower, and broccoli. Such a procedure is entirely ineffective to reduce arsenic which fruits and vegetables may have obtained by resorption from the soil and which they have incorporated into their substance. Inasmuch as an effective, enforceable and practical control of this situation is not likely, the replacement of arsenical insecticides by

less hazardous substances which disintegrate spontaneously into non-toxic forms is an urgent need.

In the meantime it appears to be desirable that public health authorities conduct an educational campaign among physicians, especially those located in industrial and mining centers and in agricultural districts in which the use of arsenical insecticides is common, concerning the symptomatology, diagnosis, and therapy of acute and chronic arsenical poisoning and the conditions of exposure to arsenicals. Postmortem examinations of all cases suspected of arsenical poisonings should be made whenever possible in order to determine not only the well recognized hazard of cutaneous malignancy, but to study also the controversial question of arsenical malignancies in other organs, such as the lung, mouth, esophagus, stomach, intestine and liver.

XVI. MEDICO-LEGAL ASPECTS

Arsenical dermatosis and cancers are recognized compensable occupational diseases in a number of countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, France, Germany, Great Britain, Italy, Japan, Mexico, Sweden, Switzerland, and in a number of states of the United States [New York, New Jersey, Pennsylvania, Ohio, Illinois, Wisconsin], Porto Rico). The effectiveness of the laws in force in some of the countries and states named is impaired, however, as far as the protection of the worker is concerned, by the existence of limiting time clauses.

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b. Salpeter—Sodium Nitrate

In 1926, Prunés observed 6 cases of skin cancer (2 basal cell carcinomas, 2 spinous cell carcinomas, 1 intermediary type, 1 unknown variety) among workers in the salpeter industry of northern Chile. During the years 1930 to 1935 Guzman had under his care six additional cases of cutaneous malignancy among individuals of this occupational group, all of whom had been engaged for many years in carrying bags filled with salpeter. In 1939 this investigator reported on a total of 17 cases of skin cancer in nitrate workers. These men had shown over an extended period of years multiple dyskeratotic lesions, having the form of plaques and nodules, located on their trunks and extremities (hands and feet). One or several of these callosities had exhibited, suddenly, after years of slow growth, highly malignant qualities.

The age range varied from 37 to 75 years (37, 53, 56, 58, 72, 78), and the exposure period was upward from 28 years to more than 50 years. Several of the men had followed this particular occupation since childhood. The dyskeratotic lesions preceded the malignant development by a varying number of years (25 years or less). The tumors were of verruco-papillomatous growth showing a tendency to break down and ulcerate. Histologically, they were squamous cell carcinomas, sometimes showing a high degree of anaplasia. Their location was on exposed parts or readily traumatized portions of the skin (forearm [2], heel, sole of foot, internal ankle, sternum, humero-scapular region). In one case, there were three tumors present.

Although these cases are the only ones observed among approximately 50,000 workers similarly exposed, Guzman believes that these cutaneous malignancies are the result of an occupational exposure to some chemical contained in salpeter (chemical irritation), probably accentuated by traumatic factors (noted in two of the six tumors). His attempts to reproduce these conditions in rabbits by the repeated application of a 20 per cent solution of salpeter to the skin were unsuccessful.

The chemical analysis of crude salpeter, which is mined as a brown to grey material, colored by an admixture of iron oxide and bituminous substances, shows that it is composed of sodium nitrate, potassium nitrate, sodium sulfate, sodium chloride, double salts of sodium nitrate and sodium sulfate, magnesium sulfate, and in some regions also potassium chlorate and perchlorate, magnesium chloride and double salts of calcium iodate and calcium chromate. The purified salpeter is obtained by extraction and precipitation from a hot or cold solution, depending upon the method used.

The evidence so far available in support of an occupational genesis of these tumors is not substantial. None of the chemicals contained in salpeter are known to possess specific carcinogenic properties. A non-specific chronic irritation by chemicals, on the other hand, does not provide, as a rule, the proper carcinogenic stimulus. This fact is well established by numerous observations made with chemical chronic dermatosis. Without additional and detailed in-

formation concerning the amount and character of the bituminous substances contained in crude salpeter, an opinion cannot be expressed as to the rôle such agents may have played in producing cutaneous neoplasms. Also, consideration must be given to the possible action of an actinic factor, as the climate in northern Chile is dry and sunny.

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B. ORGANIC CHEMICALS—GENERAL CHEMICAL AND TECHNOLOGICAL ASPECTS

The organic chemicals incriminated in the production of occupational cancers of the skin are derived from the distillation and fractionation of coal, oil shale, lignite, bitumen, goudron, asphalt, crude mineral oil and similar naturally occurring substances, composed of mixtures of numerous aliphatic or cyclic hydrocarbons and containing not infrequently in addition to the basic elements, carbon, hydrogen and oxygen, also nitrogen, sulfur, arsenic and other elements.

While not all the products derived from these basic substances possess carcinogenic properties, and while the presence or absence of blastogenic properties in derivatives carrying identical names and used for the same purposes depends not infrequently upon the type of technical process and the chemical composition of the particular raw product employed, yet many of the fractionation and distillation products (pitch, tar, crude paraffin oil, lubricating oil, fuel oil, anthracene oil, creosote, soot) have been proven definitely to represent the primary exogenous causes of an appreciable number of industrial cancers.

The predominating practical significance of these carcinogenic hydrocarbons is based, to a great extent, upon the fact that these substances constitute the main foundation upon which modern chemical industry has been erected and that they are used to an increasing degree in the manufacturing processes and products of other industries. The number of persons coming in close occupational contact with these compounds is large and their numbers constantly and rapidly increase. The extensive employment of these substances for various purposes, such as road construction, has brought about a wide spread environmental exposure of the general population to carcinogenic agents of this type. For these reasons these mentioned blastogenic organic compounds are not only suspected, or have been shown to be the cause of certain general environmental cancers, but represent especially etiologic factors responsible for large numbers of industrial malignancies. They are the most common source of cutaneous tumors of occupational origin as well as the causal agent for industrial blastomas of the lip, mouth, lung, and eye. Some of their derivatives (aromatic amines) are incriminated in the production of cancers of the urinary tract in certain groups of chemical workers.

In addition to the outstanding practical importance which products obtained from coal and mineral oil have attained, they possess a high scientific significance. The study of the chemical composition and structure of the various carcinogenic fractions of pitch and tar, undertaken for the purpose of finding the neoplastic factor contained therein, led ultimately to the discovery and synthesis of numerous carcinogenic polycyclic hydrocarbons, and thus supplied one of the most powerful stimuli cancer research has received. The results of these investigations provided not only the means for producing cancer, experimentally, in various organs with different, chemically well defined substances, but furnished also important evidence demonstrating the existence of close chemical relations between the newly developed synthetic carcinogenic hydrocarbons and certain substances normally occurring or produced in the human body (sex hormones, bile acids, sterols, and vitamins).

a. Coal, Asphalt, Mineral Oil, Oil Shale

In contrast to the extensive studies to which the various fractions and distillation products of coal, asphalt, mineral oil, and oil shale have been subjected because of their manifest blastogenic properties, relatively little information is available concerning the cancerigenic potentialities connected with occupational exposure to the native materials (anthracite, bituminous coal, lignite, asphaltic rock, native asphalt, oil shales, and petroleum). These natural products differ greatly in physical qualities, being solids, semiliquids or liquids, and differ too in chemical composition, containing carbonaceous matter mixed with cyclic and acyclic hydrocarbons in varying proportions.

1. COAL

Coal in its various forms (anthracite, hard coal, brown coal) is mined in many parts of the world, especially in the United States, England, Germany, Belgium, Holland, France, Russia, Poland, Japan, and India. Observations made on coal miners as to the occurrence of cutaneous malignancy attributable to their occupational activity show that no reliable evidence exists that points to a specific chemical carcinogenic action exerted upon the skin through contact with coal dust. Barnewitz mentioned that in the Ruhr district (Germany), miners engaged below ground in the mining of coal used in the production of gas, developed after ten years of service pigmentary cutaneous disturbances, which consist of hyperpigmented brown to black spots involving the exposed parts especially the skin of the face and arms, sparing, however, the legs and feet. These changes vary in intensity and extent in different individuals and are never connected with hyperkeratotic lesions or inflammatory changes. They do not produce any light sensitivity, such as is observed with similar pigmentary manifestations derived from exposure to tar, lubricating oils, or anthracene. Similar observations were reported by Jordan, who claimed that even the distillation products of anthracite were innocuous in regard to carcinogen-

esis. Vossenaar reported that "pitch skin" was only occasionally encountered among the coal miners and workers of the Limburg district in Holland. Histological studies of the reported pigmented lesions demonstrated that the pigment is melanin, almost exclusively accumulated in the chromatophores of the cutis, leaving the basal cells of the epidermis unaffected (Barnewitz).

While Young and Russell did not find excessive incidence of skin cancer among English coal miners, Bettazzi reported a case of carcinoma of the hand in a coal worker who had handled, for five years previous to the development of the tumor, a coal rich in tar and pitch. After sustaining an accidental abrasion of the skin of the back of the hand by a coal splinter, this man continued his usual work for two months and frequently rubbed coal dust into the wound when attempting to clean his hands. Nineteen months after the injury the coal worker died from metastases of an ulcerative carcinoma originating in the wound. Haagensen, in his survey of the occupational cancers treated at the Memorial Hospital in New York during the years 1917 to 1930, listed sixteen cases of cutaneous epithelioma in male individuals who had had intimate occupational contact with coal. The occupation of these men was coal shoveler (cancer of the lip), coal bargeman (carcinoma of the neck), fireman (14 cases: three with carcinoma of the ear, four with cancer of the lip, one each with epithelioma of the nose, hand, eyelid, penis; three with cancer of the cheek, and of these two were basal cell tumors).

In view of the recognized mechanical irritative action which coal dust exerts upon the skin (Jordan), claims have been advanced that the potential cancerigenic effect of coal dust is not so much of a chemical nature as of a physical, chronic traumatic type. Fabry and Bockholt pointed out that there were 15,674 miners with skin diseases recorded, 1897-1921. As one hundred and twenty-six were cases of cancerous character, Fabry and Bockholt expressed the opinion that an occupational superficial mechanical irritation, caused by the coal dust, might have been a predisposing factor in the development of these cancerous lesions. Inasmuch as similarly extensive surveys from other coal mining districts are not available and because marked variations in the chemical composition of different kinds of coal exist which may elicit conceivably different reactions in exposed skin, definite conclusions cannot be drawn about the possible carcinogenic action of coal and the actual existence of industrial cancers caused by coal. The scanty evidence available at present does not favor the conception that coal dust is a chemically or a mechanically active carcinogenic agent.

II. LIGNITE

Brown coal and similar bituminous carbonaceous deposits (ozokerite, lignite) are found in Germany, Siberia, Russia, United States (Utah, Texas), Mexico, Hungary, Finland, Portuguese East Africa, and numerous other countries. They are black, brown, green or yellow colored, greasy, soft to

dry, powdery masses, whose consistency depends upon the relative content of hydrocarbons contained in a mineral matrix. These bituminous substances are employed as fuel and for the production of paraffin, oils, tar, and asphalt. Definite information does not exist as to any direct carcinogenic properties of these materials and the possible occurrence of industrial cutaneous malignancies among the miners and users of these products.

III. OIL SHALE

Shale rock, carrying mineral oils, are found in Scotland, France, Australia, Germany, Estonia and Manchukuo and are used for the production of oils, paraffin and tar. Large shale deposits, for the most part not yet mined, exist in the United States (Colorado, Utah, Montana, Nevada, California), Russia, South Africa, Mesopotamia, Syria and Chile. The chemical character of the crude oil contained in the various shale deposits differs greatly. The shale oil obtained from Scottish shale is rich in paraffins, while the oil distilled from Estonian shale is almost free from paraffins, but contains a considerable amount of creosote. Whereas the Scottish shale oil and its fractionation products are the source of a great number of occupational cutaneous malignancies, no data are available concerning the occurrence of epitheliomas among the miners of these Scottish shales or of any of the other shale deposits in other countries.

IV. ASPHALT

Native asphalts, occurring either as surface deposits in the form of ponds or lakes formed by the natural evaporation of the volatile substances of mineral oil, leave a blackish, semisolid matter consisting largely of condensation products of petroleum (Trinidad, Venezuela, Utah, Colorado, California, Palestine) or as rock formations (sandstone, limestone) impregnated with asphaltic material (Switzerland, France, Belgium, Italy, Germany, United States [Texas, Oklahoma, Alabama, Kentucky]). The chemical composition of the asphalt found in the Pitch Lake of Trinidad is, according to Ross, as follows: water and gas, 29 per cent; bitumen, 39 per cent; organic matter, 7 per cent; mineral matter, 25 per cent. The bitumen consists to 82.23 per cent of carbon, to 10.69 per cent of hydrogen, to 6.16 per cent of sulphur and to 0.81 per cent of nitrogen. This native asphalt, chemically, resembles closely the non-volatile constituents of crude oils without a paraffin base. The native asphalt must be distinguished from the so-called asphalt obtained by coal distillation and of certain types of petroleum (United States, Mexico, Venezuela) which possess a high asphaltic fraction, as these distillation products are not only chemically different from the native variety, but also display, in part carcinogenic properties. Information as to the potential carcinogenic qualities of *native* asphalt is available only in connection with the asphalt mined from the Pitch Lake in Trinidad. Ross, who cited the observations by physicians who were employed by the company handling the operations at Pitch Lake and who supervised

the workers, stated that no cutaneous epitheliomatous lesions had been seen in the workers engaged in the mining and the transport of the asphalt.

V. PETROLEUM

Petroleum, naphtha, or crude mineral oils is found in many parts of the world (United States, Mexico, Venezuela, Borneo, Sumatra, Persia, Iraq, Russia, Galicia, and Rumania). The chemical composition of mineral oils varies greatly with the field of origin. Even oils from locally closely related fields may be radically different in chemical respects. Crude mineral oils consist of a mixture of short and long chained hydrocarbons (paraffins), cyclic and polycyclic hydrocarbons (naphthenes), and non-hydrocarbon substances (sulphur, resinous compounds, oxygen, nitrogen) in varying proportions.

On the basis of the chemical character of the residual substances remaining after their distillation, the mineral oils are divided into three main types: (*1*) oils with an asphaltic base; (*2*) oils with a paraffin base; (*3*) oils with a mixed base.

Petroleum obtained from the eastern Appalachian field (Pennsylvania, Ohio, Kentucky, New York, Virginia) is composed largely of paraffinic hydrocarbons and contains little asphalt. Mineral oils from the mid-continental field vary in composition in different regions. Oils from northern and central Texas, Arkansas, and Louisiana have a high paraffin content and contain more asphalt than oils from Eastern fields. Petroleum from Kansas, which is also mainly paraffinic in character has a still higher asphalt content, while oils from Wyoming, Montana, and Colorado are of the mixed base type with a high asphalt proportion. The petroleum obtained in the Gulf Coast fields is predominantly naphthenic, but contains upward of 10 per cent asphalt. Californian oils are mainly naphthenic, with much asphalt and practically no paraffin when originating from the northern fields, while in more recently developed southern fields oils with a considerable proportion of paraffins and much asphalt are found. The oils of Mexico and Venezuela are of the mixed type, containing both asphaltic (aromatic) and paraffinic hydrocarbons (Gruse). Caucasian petroleum consists of 80 per cent of naphthenes. East Indian varieties (Java, Sumatra, Borneo) contain, in addition to a high proportion of paraffins, benzolic and unsaturated aromatic hydrocarbons, but are free from asphalt.

Heller, according to his inquiries, noted that none of the asphaltic American crude mineral oils has ever produced a skin cancer among oil-field workers employed. Wood made the same claim as to the paraffinic oils from Pennsylvania. Oils from Indiana, Ohio, Northern Texas, Oklahoma, and Kansas, which have a mixed character, are, on the other hand, not entirely harmless in this respect (Heller). While the crude California oils have been found to be noncarcinogenic, refined products, obtained from these oils, exhibit carcinogenic properties (Twort). Petroleum from the Galician fields, containing much paraffin and little asphalt, seems to possess mild carcinogenic qualities (Ullmann),

while only hyperkeratoses, but not malignancies were observed among the workers employed in the Russian oil fields of Baku and around Grozny (Ullmann; Kolesnikow). Whereas Ullmann noted that hyperkeratotic warts were seen frequently among laborers in the Rumanian oil fields and refineries, Baader stated that, according to information received by him from Jovin, director of the Bucharest cancer center, not a single case of epithelioma has been observed among the 2,000 men employed in the four largest Rumanian refineries.

VI. COMMENT

The data presented indicate that relatively little evidence exists incriminating the basic substances from which substances are derived which are among the most potent carcinogenic agents that are active in the production of occupational malignancy. While it must be conceded that information available on this matter is more or less highly defective and, in part, unreliable, the data on hand militate against any generalizing or definite conclusions because of the marked discrepancies existing not only in the chemical composition of the various types of basic substances, but also of the materials of the same kind.

This conclusion is warranted in view of the fact that in some instances, such as with mineral oils, it was shown that the chemical differences are reflected in the types of the biological reactions produced by these substances. Thus, while an accurate evaluation of the degree of occupational neoplastic hazard connected with the handling of the basic substances is difficult, such a procedure is aggravated by the prevailing practice of blending some of these materials (asphalt, mineral oils) for some purposes (road construction, fuel) with products obtained from them or other members of this group by distillation and fractionation, and which are carried at times under the same commercial or trade name. Native asphalt, for instance, is often mixed with artificial asphalt originating from the distillation of petroleum, or it is blended with pitch or tar derived from the distillation of coal. Crude mineral oils from one native field are cut not infrequently with mineral oils of different chemical structure coming from one or several other fields or occasionally with liquid fractionation products obtained from the distillation of coal. Positive observations concerning the cancerigenic qualities of the various primary hydrocarbonaceous substances are for these reasons of more conclusive value than negative ones, which must be looked upon with some degree of reservation.

b. Pitch, Tar and Asphalt

I. CHEMICAL AND TECHNOLOGICAL ASPECTS

Apart from the natural asphalts, which represent evaporation products of petroleum or are the result of some other natural metamorphosis of mineral oils, asphalts are obtained, together with pitch, as the residues of the distillation of certain petroleums whose refining is carried out at a high temperature.

Similarly, tar, and the bulk of substances known as pitch, are residues of the distillation and fractionation of coal conducted at a high temperature. Small quantities of tar and pitch are the end products of the distillation of wood or similar vegetable matter (oils). Asphalt, tar and pitch are semi-solid or solid, black colored, sticky substances of extreme viscous and tenacious consistency, composed of a mixture of numerous hydrocarbons of simple as well as complex and, in part, cyclic nature. Because tar, asphalt and pitch possess many similar physico-chemical qualities, they are used frequently for similar purposes and often are mixed together regardless of origin.

The chemical character of tar, pitch and asphalt differs to some extent with the nature of the basic substance (coal, lignite, wood petroleum) from which they are obtained, and with the method of distillation and carbonization by which they are produced. Pitch, which is mainly the residue of the distillation of hard coal and petroleum, is a fractionation product of tar. Depending upon the degree to which these processes are carried out, there exists a soft type of pitch and a hard type, the latter containing more pure carbon and melting at a higher temperature than the soft variety (50 to 75°C). Depending upon the character of the tar used (wood tar or coal tar), pitch is a resinous or non-resinous residue.

The main source of tar is the destructive distillation of brown coal and bituminous coal, which, however, does not contain any bitumen (representing the solid and semi-solid natural hydrocarbons contained in petroleum, native mineral waxes (ozokerite, montan wax), native asphalts and asphaltites). The viscous, oily, brown-black tarry fraction distills over at a temperature of 900° to 1,200°C. The main constituents of coal tar belong to the series of aromatic hydrocarbons which range from the simplest volatile benzols to the nonvolatile complex compounds remaining in the still with the pitch.

In addition to small amounts of olefins and paraffins, tar is composed of cyclic (benzols) and polycyclic (naphthalenes, anthracenes, phenanthrenes) hydrocarbons, phenols, sulphur compounds, nitrogenated compounds, usually of basic nature (pyridines, quinolines), and numerous unidentified compounds (Bürgess and Wheeler; Odell; Taylor).

The following table, prepared by Jambon, illustrates the influence which the nature of the coal used for distillation exerts upon the chemical compo-

Origin of Coal	Light Oil	Phenol	Heavy Oil	Naphtha-lene	Residue
Wigan-Channel	9	14	40	15	22
Newcastle	2	5	12	58	23
Staffordshire	5	9	35	22	29
Silesia	5		15		74

sition of the tar, as reflected by the relative proportions of the various fractionation products which can be extracted from such tars.

Then this next table, also cited from Jambon, illustrates the effects which different methods of production exert upon the chemical composition of tar as evidenced by the proportional relations of the different fractions obtainable from tar.

	Gas Tar	Dry Distillation	Water-Gas Tar
Ammonia	4.0	4.3	6.22
Light Oil	4.0	30.32	25.34
Heavy Oil	32.0	38.13	32.68
Paraffin	—	—	13.68
Asphalt	56.0	18.75	16.03
Gas	4.0	8.5	6.20

Numerous factors influence both the yield and the composition of the tar produced, in particular the kind of coal carbonized, the type of retort setting used, the temperature to which the coal is heated; and the manner in which the heat is applied (*Encyclopedia Britannica*). The following types of tar are distinguished for these reasons: (*1*) wood tar; (*2*) lignite tar; (*3*) gas works tar: (*a*) tar produced in horizontal retorts and (*b*) tar obtained in vertical retorts; (*4*) blast furnace tar; (*5*) coke-oven tar; (*6*) producer-gas tar; (*7*) water-gas tar; (*8*) synthetic and experimental tars resulting from the conversion of pure hydrocarbons, isoprene and acetylene (Kennaway) into tarry substances under the influence of high temperatures or being the products of the destructive carbonization of organic matter, such as skin, hairs, bones, cholesterol and tobacco (Kennaway; Roffo; and others). Tar of types 3 to 6 are manufactured from coal. Wood and vegetable tars have chiefly medicinal importance (ointments, hair lotions, soaps), while the coal tars are of preeminent industrial significance.

Wood and vegetable tar, produced by the carbonization of wood or vegetable matter under the exclusion of air, has an acid reaction, in contrast to the alkaline reaction of coal tar, because vegetables contain little ammonia (which is responsible for the basic character of coal tar), paraffins and naphthalenes. In vegetable tar there are, on the other hand, acids of the formic acid series as well as alcohols, aldehydes and aliphatic ketones. Tar prepared from resinous trees contains lower phenols as well as polyphenols, acetone, acetic acid, methyl alcohol, methyl acetate, and their homologues.

Lignite tar is obtained by heating lignite in generators built of brick. The older retorts used for this purpose were of the horizontal type, requiring a discontinuous type of operation and a higher temperature than the vertical retorts introduced about 1858, which enabled a continuous operation and the

use of lower temperatures (400°C in the upper part, 600°C in the lower portion).

While in most lignite plants the more efficient vertical generators have been introduced, there were horizontal high temperature retorts still in operation in 1892 (Kennaway). The vertical generators, which are filled with lignite, have a grate at the bottom through which air and steam is pressed through the burning lignite. The heat generated in the lower part causes the production of coke, which has a temperature from 360° to 400°C, and the development of tar fumes from the coal in the upper portion which are condensed. Brown-coal tar, thus obtained, is redistilled for fractionation. During this process, *first*, paraffin free components of the tar are driven off, representing about one-third of the material. *This phase is followed* by the recovery of crude soft paraffin, while *the last and third fraction* of the volatile substances distilling over consists of hard paraffin.

Tar coke, containing still some of the hydrocarbons, is the residue of the distillation. The distillation products are treated further, for purposes of purification, by redistillation and rectification with sulfuric acid and sodium hydroxide, which are added for the destruction of undesirable impurities.

From the waste sulfuric acid, which appears as a viscous, dark colored mass, resins are produced, which are used in the manufacture of asphalt. A second product of the preliminary treatment of the paraffin fractions with sulfuric acid and sodium hydroxide is sodium creosote, which combined with acid resins yields, following distillation, creosote oil and asphalt. The crude paraffin, after having been freed from its tarry fraction, is then sent through rotating coolers and filter presses so as to obtain a separation between the various oily admixtures and the paraffin proper. Similar tars are produced in the manufacture of ceresin from ozokerite by the asphalt method.

Gas-works tar is one of the three main products resulting from the carbonization of coal under the exclusion of air carried out at a temperature of 800° to 1,000°C (horizontal retorts with high temperature tar) or of 400° to 500°C (vertical retorts with low temperature tar) yielding illuminating gas and fuel gas containing, before purification, hydrogen sulfide, ammonia liquor and tar. The separation of the three fractions is accomplished by condensing the fumes and vapors generated in the retorts. The two liquid portions are collected when the hot gaseous fumes and gases are conducted into huge tanks of sheet iron construction filled partially and sealed with water. The high boiling aromatic and aliphatic compounds are then precipitated, carrying along some of the lower boiling light and medium oils, and accumulating at the bottom of the container as an oily, almost black substance. The water overlying this tar absorbs and dissolves the ammoniacal vapors and is thereby converted into ammonia liquor. The tar is mixed with solid oxidation products which are carried along during the distillation and which, later on, settle in the pipes and on the walls of the basin as hard pitch.

In old gas plants, the tar has to be removed directly from the basin from time to time. In gas works of more recent construction, the tar flows through an overflow or, when a special faucet is opened, into a larger general collecting basin, where the tar from several or all retorts present in the gas works is collected.

With this newer system, the solidified tar has to be chopped out and removed at longer intervals than formerly. In new gas plants operating with vertical retorts which permit a continuous feeding of coal and removal of coke, the tar is blown directly, before it can solidify, into a collecting basin with the aid of a strong jet of water. The gas is freed before it enters the gas tanks from tarry impurities by passing through special tar separators and tar towers, which must be cleaned from tar several times a year. The tar remains in the large collecting basin until tar and water have separated and can be pumped, without entailing any direct contact of the workers doing such work with the tar, into tank cars for removal to tar distilleries. This crude tar contains 2 to 5 per cent of ammonia water.

Crude tar is used as a fuel for open hearth furnaces in steel mills; for the construction of roads (macadam roads, mixed with gravel); in the production of roofing paper (formerly exclusively, and more recently, as a diluent of pitch); as a protective coating of pipes, lumber; as an insulation and waterproofing of concrete walls and brick walls; as an ingredient of metal paints; as a core compound; in the manufacture of carbon; as a binder in the briquette industry and as a basic material for numerous substances obtained by fractionated redistillation and used in chemical industries.

For the purpose of redistillation and fractionation, tar is charged into a still which is heated with coal or surplus gas and which is provided with a mechanism controlling the temperature inside of the still. During the first phase of the distilling process, when the tar is heated to a temperature of up to 105°C (first running), a very light mobile oil composed of benzol, toluol, and similar readily volatile substances, mixed with small amounts of phenol and bases, is obtained. The completion of this step is indicated by the fact that the specific gravity of the residue rises. The temperature in the still is then increased to 220°C. The "light oil" distilling over during this stage consists of *paraffins* (pentane, hexane, and homologues); *olefins* (pentene, hexene, heptene, octene); *cyclic unsaturated hydrocarbons* (cyclopentadiene, tetrahydrobenzol, dihydrobenzol, dicyclopentadiene); *aromatic hydrocarbons* (benzol, toluol, methyl benzol, p-xylol, o-xylol, mesitylene, tetramethyl-benzol, styrol, indene, methylindene); *nitrogenous bodies* (basic: pyridine, alpha-, beta-, and gamma-picolin, aniline, trimethyl-pyrodine; neutral: acetonitrile, benzonitrile, pyrrol); *oxygenous bodies* (acetone, cumarin); *sulfurogenic bodies* (carbon disulfide, thiophene, thiotoluene, thioxene). This fraction represents, usually 7 to 8 per cent of the tar.

The third fraction is obtained at a temperature of approximately 240°C, at

which the so-called "middle oil" or "carbolic oil" comes off, representing 8 to 12 per cent of the tar. This middle oil is composed of *hydrocarbons* (pentamethyl benzol, hexamethyl-benzol, hydrated naphthalene, paraffins); *bases* (toluidine, quinoline, isoquinoline); *oxygenous bodies* (neutral: methyl-cumarone, acetophenone); *phenols* (phenol, o-, m-, and p-cresol, xylenols).

The fourth fraction distils over at 270°C and is called "heavy oil" or "creosote oil." It is a greenish fluorescing oil representing 10 to 12 per cent of the tar. Heavy oil contains *hydrocarbons* (naphthalene, alpha- and beta-methyl-naphthalene, dimethyl-naphthalene, diphenyl-naphthalene, paraffins); *bases* (methyl-quinolines, dimethyl-quinolines, thionaphthalenes); *phenols* (alpha-naphthol, beta-naphthol, diphenyloxide); cresol; anthracene. This fraction is used as crude creosote.

The fifth fraction, obtained at a temperature of around 300°C, is about 3 per cent of the tar and is known as "anthracene oil" or "green oil." Its composition varies with the temperature at which the final distillation is carried out, and this depends upon whether a soft or a hard pitch is desired as residue. The anthracene oil is a mixture of *hydrocarbons* (fluorene, phenanthrene, anthracene, methyl-anthracene, fluoranthrenes); *nitrogenous substances* (*basic:* acridine and bases of unknown constitution; *neutral:* carbazoles, phenylnaphthyl-carbazole, indol); *phenols* [of unknown constitution] (Ullmann, F).

Inasmuch as the temperatures, at which these various fractions are obtained, differ to a certain degree in different plants, corresponding variations in the chemical composition of the individual fractions occur. An additional important factor controlling the chemical character of the fractions and their relative quantities is the type of tar used, i.e., whether a low temperature tar (vertical retort tar) or a high temperature tar (horizontal retort tar) is distilled. Vertical retorts, owing to the presence of paraffinoid substances and tar acids, yield a thinner tar than do horizontal retorts. Upon distillation, vertical retort tar leaves a smaller quantity of pitch than high temperature tar (50 to 70 per cent).

Low temperature tar consists of (*a*) paraffins, olefins, and naphthenes; (*b*) aromatic compounds, chiefly phenols which make up 50 per cent of the tar (carbolic acid, cresols, xylenols, pyrocatechins, acid resins, alpha- and beta-naphthalenes and other naphthalene derivatives, anthracene in small amounts, benzene in small quantities; (*c*) toluidins; (*d*) free carbon (2 per cent); (*e*) pitch (20 to 40 per cent).

High temperature tar, on the other hand, contains (*a*) paraffins in negligible quantities, olefins in insignificant amounts, naphthenes in a few units per cent; (*b*) phenols (less abundant) and carbolic acid (in larger amounts); (*c*) aromatic compounds other than phenols (benzene, naphthalene, anthracene, phenanthrene and others) which are either entirely absent or present in only small quantities in low temperature tar; (*d*) free carbon (17 to 30 per

cent). The amount of anthracene in horizontal retort tar is usually about four times that present in vertical retort tar (Kennaway; Lung; Warnes; Odell; and others).

The fundamental difference between low temperature and high temperature tar is represented by their relative content of cyclic hydrocarbons. This phenomenon is brought about by the fact that aromatic substances are formed from aliphatic compounds under the influence of heat. The higher the temperature at which a tar is produced, the higher is its content of cyclic substances (benzene, toluene, xylene, phenols, naphthalenes, anthracenes, pyridines). Some of these compounds are therefore absent in low temperature tar. The chemical transformation of aliphatic constituents into aromatic ones apparently starts at a temperature of above 700°C to 800°C, when a sudden and large increase in the hydrogen evolved is observed together with the appearance of naphthalenes, while the evolution of gaseous olefins, which reaches its maximum at 550°C, practically ceases together with a sharp fall in the amount of methane formed (Kennaway). This investigator suggested that the formation of aromatic compounds may be due to a condensation of olefin molecules under the liberation of hydrogen.

The ammonia liquor contained in tar consists of ammonia, ammonium carbonate, ammonium cyanate, ammonium sulfide and ammonium chloride.

The residue of the tar distillation, pitch, is obtained at a temperature of about 400°C. Pitch, in turn, can be decomposed upon fractionation into a benzol soluble part containing pyrene, chrysene, truxene and hydrocarbons of unknown nature and into a benzol insoluble fraction consisting of carbon. Pitch is collected in modern tar distilleries in calcimined forms, which can be removed readily. In many older plants the pitch is pressed into high tanks from which it is transferred into railroad cars, the removal therefrom entailing usually hacking and shovelling, and resulting in the production of a large amount of pitch dust. In more up-to-date factories the pitch is discharged, while still soft, directly into tank cars in which it can be heated through steam pipes to enable the reliquification of the pitch. Then this substance can be pumped from the tank car at some distant point of consumption without handling and dust production.

Pitch is used in the manufacture of briquettes, corkstones, cement; for the insulation of electric appliances; for the production of storage battery cases; in the manufacture of roofing paper; for the surfacing of roads; for lacquers; and waterproofing of walls.

Blast furnace tar is produced in certain metallurgical operations (iron and steel mills). While coke and anthracite, used in most blast furnaces, do not give rise to the development of tar, the so-called "splint-coal," employed in furnaces of Scottish iron works and in those located in the north of England, causes the production of tar. This particular coal is used because it does not

soften on heating in the furnace, and because it forms directly a strong coke which is not crushed by the weight of the ore. The upper portion of the blast furnace, which acts like a coke-oven, contains gas, tar and coke. The tar is recovered from the escaping gases by condensation. Blast furnace tar possesses three characteristic qualities: (*1*) presence of higher paraffins in appreciable amounts; (*2*) abundance of phenols other than carbolic acid (cresols, chiefly m-cresol); (*3*) small amounts of benzene, naphthalene, anthracene, xylenols, (chiefly m-xylenol); pseudo-cumenol; alpha- and beta- naphthol, tolulene, xylene, trimethylbenzenes. Inasmuch as the temperature increases in the furnace from the top downward, the existing conditions favor a low temperature carbonization (Kennaway).

Coke-oven tar is produced when high grade bituminous coal is converted into coke in Kopper or Viputte ovens by carbonization at temperatures as high as 1,200° to 1,400°C. Coke-oven tar is similar in chemical composition to tar obtained from horizontal retorts in gas works, as in a coke oven packed closely with coal in the cooler portion, a good deal of the tar vapors formed there is forced subsequently through hotter regions and causes thereby the development of a tar which resembles closely that generated in a lightly charged horizontal retort. Coke-oven tar is more liquid than gas works tar.

Producer-gas tar is only obtained when, in the production of the producer gas, a fuel is used from which tar can be formed. While the distillation of anthracite and coke used for this purpose does not yield tar, this substance is developed as a by-product when peat, lignite, oil shale or bituminous coal are employed. Producer gas tar contains much water and free carbon with small amounts of oils.

Water-gas tar is a by-product of the manufacture of water gas used for purposes of illumination. Water gas is produced by spraying steam and coal oil (petroleum fraction) over red hot fire bricks, whereby the coal oil is cracked and water gas and water-gas tar are formed. Water-gas tar is therefore not a coal tar, but a complex petroleum tar. It contains paraffins, small amounts of tar acids and yields little pitch upon fractionation. The gas obtained from cracked oil is usually mixed with the gas produced by passing steam over hot coke or anthracite, resulting in the development of a gas composed of hydrogen and carbon monoxide. This mixture, called carburetted water gas, is used mainly for industrial purposes.

Shale oil tar is produced in the roasting process of the shale ore which was carried out originally (after 1850) in horizontal retorts, but, since 1868, to an increasing degree in vertical retorts. The temperature used during this procedure varies from 510° to 704°C, and results in the development of a low temperature tar. This tar is subjected subsequently to distillation and fractionation in the manufacture of various kinds of semi-refined and refined oils, and of paraffin. The shale oil tar is composed of paraffins, olefins, naphthenes,

benzene, toluol, xylol, purine, chrysene, phenol, alpha- and beta-cresol, xylenols, pyrocatechin, pyridine, quinolines and sulfur compounds (Ross).

Asphalt is the residue of the distillation of asphaltic, paraffin poor or paraffin free types of petroleum. This residue is also known under other names, such as tar, pitch, goudron, mazoute. A coke-like substance remains from the distillation of a crude mineral oil rich in paraffins. Asphalt is used for road construction (macadam roads); oiling of gravel roads for dust prevention; admixture to cement; water-proofing of walls; roofing, manufacture of storage batteries, wall boards, flooring, sheathing, lacquer, paint, varnishes, enamel, cement, moisture proofing of wrapping paper, insulating products, moulding composition, impregnation of shingles; as an addition or substitute in the rubber industry; and as asphalt oil, as a remedy of sheep eczema. The hard goudron is often mixed with high boiling mineral oils or softer petroleum asphalt.

II. HISTORICAL AND GEOGRAPHICAL ASPECTS

The first case of occupational tar carcinoma of the skin was described by Volkmann in 1876 in a worker employed in a tar distillery located in the lignite district in the neighborhood of Halle, Saxony. While the subsequent cases of occupational cancer reported from this industrial district were related to the production of paraffin obtained through the fractionation of the lignite tar, the rapidly growing industrial development of Germany with its establishment of coal tar plants, coke ovens, briquette factories, and numerous other industries using tar and pitch in the manufacture of their diverse products, furnished during the following decades many new and more extensive opportunities for an occupational contact with tar and pitch and for the occurrence of industrial cutaneous neoplasms caused by these substances.

The second case of occupational tar cancer in Germany, was not placed on record until 33 years later by Zweig, who observed three cases of multiple tar papillomas in workers exposed to hard coal tar. A scrotal manifestation in one of these men proved to be malignant.

In 1911, Rambousek mentioned the occurrence of cutaneous cancer, especially affecting the scrotum, in hard coal tar workers. The rarity of anthracite tar cancer among German workers was emphasized by Leymann, who attributed this scarcity to the fact, that in the anthracite briquette plants in Germany (Upper Silesia) elaborate technical and sanitary precautions were long ago effected (1896). This investigator conceded, however, that tar and pitch dermatitis continued to occur among the workers employed in briquette plants and related occupations (stokers of railroad and ship engines, workers in corkstone factories in Upper Silesia as well as in the Rhenish-Westphalian industrial district). Four cases of tar cancer in coke-oven workers were added by Leymann to the German list of these neoplasms. Their actual number was apparently at that time (before 1917) already much greater, as this investigator mentioned that during a period of 5 years there had occurred in Germany

2 tar cancers per year among 2,500 workers employed in 65 hard coal briquette plants, making a total of ten cases from this source alone. In a review of occupational cancers published by Koelsch in 1924, reference was made evidently to the same cases without adding any new ones. In the same year Lennhoff (1924), on the other hand, increased the number of occupational tar and pitch cancers in Germany by three cases. During the course of the next fifteen years, Teutschlaender reported from time to time on the occurrence of these tumors among German workers, which he found especially prevalent among men working in briquette plants, while the workers of gas works were practically free from occupational tar cancer, according to his observations made in a larger number of factories in western Germany. Teutschlaender added a total of nine new cases of pitch cancer occurring among patent fuel workers. Oppenheim increased in 1929 this number further by four cases found among 24 men employed in an establishment handling tar. In the following year Lehmann mentioned the occurrence of tar warts in two workers engaged in the tarring of roads, while Brenner observed in the following year a case of tar cancer in a man working in a tar distillery. During the last decade additional cases were reported by Beintker, 1; Epstein, 1 (1930); Weiss, 1 (1931); Fuss, 1 (1932); Büngeler 1 (1934); Bering and Zitzke, 2 (1935); Staemmler, 20 cases during 1931 to 1934 in Germany placed officially on record (1936); and Lauchs, 3 (1938).

The total number of tar and pitch cancers of the skin of occupational genesis which are recorded for German workers since 1875 is sixty-three. This incidence is astonishingly low because at least a few of the cases included in this number have been counted in all probability twice. It cannot be assumed, however, that this figure reflects in any way the actual status. Lubarsch stated in 1922 that 3 to 5 per cent of those tar workers who showed tar dermatitis had a tar malignancy. Staemmler noted that during the period from 1931 to 1934, there occurred an average of five cases of this industrial neoplasm a year in Germany. In 1938, Lauchs reported in one single factory engaged in the manufacture of insulation plates (corkstone) the occurrence of three cases of pitch cancer. Lauchs moreover obtained information concerning a previous occurrence of cutaneous malignancies among the workers of this plant. During the years 1926 to 1937 four additional histologically confirmed cases of carcinoma of the skin were seen in workers employed in this particular plant by physicians of the community in which the plant was located. It is improbable that these seven cases represent the entire number of occupational cutaneous malignancies produced among the workers employed in this factory, as Lauchs noted that the management of the factory did not permit the examination of all the workers employed.

Inasmuch as Teutschlaender recorded similar experiences in regard to the cooperative spirit displayed by the management of factories in which tar and pitch cancers had occurred, it may be concluded that no reliable and complete

information is available concerning the incidence of tar and pitch cancer in industrial workers in Germany.

The evidence on hand, however, suggests that this occupational neoplasia is not unusually frequent in Germany considering the number, size and various types of factories in which tar and pitch are handled. Carozzi noted that in 8 Austrian factories (3 tar plants, 2 gas works, 1 briquette factory, 2 petroleum distilleries employing all together 1,675 workers exposed to tar, pitch and oil) the examination of 145 employees showed that 6 had occupational cancers, of which 4 were caused by tar. There were 3 additional cases suspected of tar malignancy. The four tar cancer cases were found in a tar plant employing 70 workers, whereas 82 of the 145 examined workers had pitch-, tar- or oil-skin.

The discovery of industrial tar cancer was reported in France one year after this condition was first described in Germany. Manouvriez observed in a tar distillery 9 cases of tar cancer during the years 1876 to 1877. Following this important observation there elapsed 33 years, just as in Germany, before this occupational neoplasia was again recorded. In 1909 Pellier reported two additional cases of tar cancer. Then 5 years passed before 3 cases of pitch cancer were described by Jaqué and Sluys in 1914. Thibierge reported 2 cases in 1918. Courmont, in 1924, mentioned one case published by Bonnet and a second case observed by Berard and cited by Poty in 1923. When Kennaway referred in 1925 in his treatise of tar and pitch cancer among English workers to the incidence of this disease in other countries, he mentioned two unpublished cases which had occurred in France during 1909 to 1925. During the same year (1925) two cases were added to the list of tar cancers in France, one by Leclercq and Cordonnier and the second by Huguénin. The following years brought the publication of several additional cases: Milian and Garnier, 1 case in 1928; Nicolas, Lacassagne and Rousset, 1 case in 1931; David and Brassart, 1 case in 1932; Barthe, 4 cases (pitch) in 1937.

Carozzi mentioned that Roussy collected information concerning one definite and two doubtful tar cancers, which had occurred since 1918 among the workers of a tar distillery located in the region of Arras. Five to six additional cases were said to have been observed among the workers of a similar factory in the same part of France, while five cases were recorded from a factory near Douai (one of which involved the scrotum) (1925). Roussy was quoted to have seen or heard of numerous tar warts and epitheliomas among tar workers employed in factories near Toulouse (1910-1925). Poty, on the other hand, could not find any tar cancers among the workers of tar distilleries and related industries situated in the Department Rhône and adjacent regions. A total of 55 cases of industrial tar and pitch cancer of the skin have been placed on record in France from 1876 to 1937.

From Switzerland, Schürch reported in 1930 the occurrence of pitch cancer among corkstone workers (2 cases). This number was increased during the following years: Schürch (1931), 2 cases; Schürch and Schrafl (1931), 1 case;

Barkmeyer (1939), 4 cases. Miescher noted in 1934 the observation of 4 tar cancers. There is thus a total of 13 pitch and tar cancers found in Switzerland since 1930.

Koelsch mentioned in 1924, that one case of pitch cancer had been observed in Holland in 1913. De Vries added in 1928 three pitch and two tar cancers which had been seen during the period from 1913 to 1927, and Kranenburg found one scrotal cancer and 136 cases with tar warts among 243 briquette plant workers, making a total of seven recorded cases for that country.

While Ullmann had stated in 1922 that many cases of tar and pitch carcinoma of the skin occurred among the workers of Belgian briquette plants, during the years 1917 to 1921, de Laet asserted in 1934, that there were no occupational tar cancers on record in highly industrialized Belgium. This rather amazing announcement was contradicted in 1940 by the investigations of Uytdenhoef as well as Firket and Malter. Uytdenhoef found, in 1934 to 1939, 18 cases of skin cancer among 400 pitch and tar workers in Belgium in addition to 16 cases of "early cancers" and a considerable number of warts. Firket and Malter observed two fatal cases of tar cancer in workers with 20 to 26 years exposure to this substance in addition to 16 pitch workers with warts.

From agricultural Hungary, Doleschall reported in 1928 the occurrence of one case of pitch cancer. Goyanes recorded from Spain one case of this industrial neoplasm in 1927, as did Ball from Ireland in 1885. The observation of a pitch cancer of the palm of the hand in a Russian glass-blower was noted by Epstein in 1930.

The first case of tar cancer in Italy was described by Carelli in 1924, after Olivier had mentioned in 1902 the presence of scrotal carcinomas among Italian asphalt workers. This observation, however, was not confirmed by Carozzi who noted specially the absence of cancer among the asphalt workers in Sicily and the Abruzzi. In a survey made by Truffi, this investigator found a total of six tar cancers among "asphalt" workers which had occurred between 1910 and 1925. A seventh case of tar cancer was added by Picardi in 1926. This number was increased further by one case in 1928 (Lazzarini), and by four cases in 1931 (Calgaris, 1; Bettazzi, 3). Bettazzi discovered the three cases while making a thorough study of the industrial cancer situation by surveying the gas plants in Milan, Venice, Florence, Turin, Rome, Naples. There is thus since 1910 a total of 12 industrial pitch and tar cancers of the skin placed on record in Italy.

The whole of continental Europe has reported not more than 130 cases of this industrial neoplasm since its first description in 1875.

This relatively small number of industrial pitch and tar cancers of the skin reported from the countries of continental Europe is in stark contrast to the appalling incidence of these occupational neoplasms observed in England, Wales and Scotland, especially since the beginning of the present century. The

first cases of this type were recorded in Great Britain by Butlin in 1892, who observed scrotal cancers in 7 tar workers. Fifteen years later (1907), Wignal placed on record 38 cases of pitch cancer of the skin affecting workers employed in patent fuel plants. During the following year, Oliver added 3 cases of skin cancer observed in workers handling coal grease, 2 cases in asphalt workers and 6 to 7 cases in tar workers. Two cutaneous epitheliomas occurring in gas house workers were seen during the years 1902 to 1910 by Brockbank and Stopford at the Manchester Royal Infirmary. Hope noted the occurrence of 64 pitch cancers in South Wales during the years 1914 to 1918, and mentioned the presence of tar epitheliomas among the stokers employed there in industrial establishments. O'Donovan reported in 1920 his observations on 2 pitch cancers and 8 tar cancers, and added, in 1929, 18 tar cancers which had been treated between 1903 to 1920 in London hospitals.

Legge placed in 1922 the total number of tar, pitch and paraffin cancers which were observed before 1920 at 89 cases. Bridge and Henry mentioned that there were recorded 8 fatal cases of coke-oven tar cancer and 7 cases (1 fatal) of producer-gas tar cancer during 1912 to 1926. The occurrence of 7 scrotal cancers in workers exposed to tar was noted by Southam and Wilson in 1922. Sladden recorded 41 cases of pitch cancer among briquette plant workers during 1918 to 1925. This investigator mentioned that of 125 pitch workers with specific pitch lesions of the skin, 33 had malignant cutaneous reactions. Downing reported seeing between 1922 to 1930 73 pitch workers with papillomas and 14 with epitheliomas.

In addition to these observations from individual investigators covering more or less locally restricted regions or industries, there are the official data issued by the Chief Inspector of Factories and the information supplied by Kennaway concerning the incidence of this industrial neoplasm in England and Wales. During 1920 to 1923, 100 cases of pitch cancer and 34 cases of tar cancer occurred, according to official data, in workers in England and Wales. Bridge, and Bridge and Henry, supplemented these data in 1930 with the information that, during 1920 to 1927, 163 cases of pitch cancer, 202 cases of tar cancer, and 54 cases of pitch, tar, creosote and anthracene cancer had been recorded with the Home Office, while, during the year 1928, 175 cases of epitheliomatous lesions from occupational contact with mineral pitch tar, 20 cases from pitch, and 40 cases from tar exposure were notified. The corresponding figures for the year 1929 were, according to Bridge, 27 cases of pitch cancer and 60 cases of tar epithelioma. The same official source noted for the years 1933 to 1937, 146 pitch and tar cancers, 240 epitheliomas in workers of tar distilleries and 85 epitheliomas in gas works employees, making a total of 471 cases during 4 years.

Individual reports from recent years mentioned the occurrence of tar cancer by Goulden and Stallard (1933) and of three malignant lesions among numerous benign pitch warts treated at the Radium Institute in London

(1938). While the official obligatory notification of cutaneous malignancies from tar and its derivatives with the Home Office did not function properly during the first years following the introduction of this law, these reports have become increasingly reliable and complete in the past ten years, and thus reflect more and more the actual conditions existing in England and Wales. The data compiled demonstrate in an unequivocal way the high incidence of tar and pitch cancers in the British Isles. Inasmuch as there has not been any appreciable decrease in the number of observed cases (Sladden) in late years, precautionary and control measures so far taken seem to have been largely ineffective in checking the further occurrence of a preventable industrial neoplasm, which has involved since its first observation in 1892 a total of more than 1,400 individuals. This is quite an impressive figure, if consideration is given to the fact, that a considerable number of cases have obviously escaped observation and have not been recorded before the year 1925.

Koinuma reported from Japan the absence of cutaneous tar cancer among workers employed in industries producing and handling tar (1930). This observation was confirmed by Nagayo and Kinosita in 1940, who noted that occupational cancers have not been observed among the workers of the numerous gas, tar and tar by-products manufactures in Japan, because these workers were accustomed to great cleanliness.

Itoh (1925), on the other hand, mentioned the occurrence of cancer of the abdominal wall and thigh especially in women carrying a metal container (kairo) heated with charcoal, similar to the kangri in Kashmir, and carried under the cloak to keep warm. While it is usually contended that the resulting cancer is a so-called burn cancer, it appears to be more likely that the carcinogenic agent is a tarry distillation product of woodcoal, the action of which is enhanced by small and repeated burns. Kairo and kangri cancers are most likely mainly tar or soot cancers. Neve and Vaughan have recorded a great number of such cancers among the shepherds in Kashmir, who employ for this purpose an earthenware vessel filled with hot charcoal (1923, 1924, 1929, 1930). Within 50 years Neve observed more than 2,000 such kangri cancers in Kashmir.

Kangri is an earthenware bowl 6 inches or more in diameter and surrounded by a basket work with a wicker handle. This bowl is filled with hot wooden embers, which are covered with a layer of ashes, and sprinkled with water to prevent a too active combustion. This heating appliance is carried by the poorer class against the skin under a single garment similar to a smock frock. The temperature of the part of the vessel touching the skin may reach 150°F. The charcoal is generally prepared from the wood of the plane, willow, and witch hazel trees, and rarely from the pine, which is too smoky. Volatile combustion substances may possibly play a rôle in addition to burns. The common site of these cancers are the inner aspect of the thighs and the anterior surface of the abdomen below the umbilicus. Although a similar heating appliance,

named "scaldino" is used in Italy, no instance of cancer resulting from its use has been recorded as yet (Henry, 1930).

From Australia, Hunt (1933) reported the occasional occurrence of cutaneous epitheliomas among the tar workers employed at road construction and maintenance. The reason for the low incidence of this industrial neoplasm in Australia is presumably the general use of a vertical-retort tar possessing a low carcinogenic potency. Especially in the northern and southern regions of Africa where large cities and extensive modern industrial establishments and road constructions are found, no data are available concerning the incidence and existence of tar cancer in Africa.

The recorded occurrence of tar and pitch cancer from the Americas has been restricted to the United States. From this country Schamberg described 5 cases of cutaneous epithelioma in tar workers after (1910) Lueke briefly mentioned in 1907 the occurrence of epitheliomas in carbon workers. Stengel and Austin placed a sixth case on record in 1916. When Wood conducted 13 years later a survey of gas works (6), briquette plants (5), and coke by-product plants (6) in Pennsylvania (1929), he could not find a single instance of cutaneous malignancy caused by tar or pitch and only an occasional instance of tar or pitch warts among the workers employed in the plants investigated. The value of this observation is impaired seriously as the majority of the workers examined had only been employed in these operations for a few years (1 to 3) and, therefore, had not been exposed sufficiently long to respond with any cancerous reactions in case an exposure to suitable agents had been present.

A similar investigation was made by Heller (1930), who reported negative observations regarding the occurrence of skin tumors among the workers of gas plants of various large cities (New York, Philadelphia, Chicago, Pittsburgh, and Milwaukee) as well as among the employees of coke-oven plants, briquette factories, tar distilleries, and tar roofing paper factories.

Heller, however, noted one exception, a plant in Cleveland engaged in the manufacture of carbon black and dry battery cases. There had occurred over a period of ten years preceding this survey a total of 21 cases of cutaneous malignancy (19 pitch cancers, 2 tar oil cancers) in this establishment. Fifteen of these cases were caused from exposure to gas-works pitch, while four cases resulted from contact with coke-oven pitch. Heller claimed that the scarcity of tar and pitch cancer in the United States was attributable to the fact that, in general, the less dangerous coke oven tar is used while the more carcinogenic gas house tar is only employed as an admixture to the former. It is unfortunate that Heller did not apparently investigate the workers of the gas plants and coke ovens, which produced the carcinogenic tar responsible for the cases observed in the Cleveland factory. In addition to the cases seen in Cleveland, Heller found 12 recorded instances of tar cancer observed at the Memorial Hospital in New York between 1920 and 1927, and seven more cases of this same

disease at the Skin and Cancer Hospital, New York, between 1926 and 1928 (11 gas house workers, 1 coke-oven tar worker, roofers).

In a study of occupational cancers observed at the Memorial Hospital between 1917 and 1930, Haagensen reported 20 cases of tar and pitch cancer. In a recent investigation on the etiologic relationship of occupation to malignancies of the eye and its adnexae, Lane (1938, 1939) pointed out that workers in tar and pitch exhibit an excessive liability to neoplasia of the ocular adnexae, especially of the lids. Foerster and Schwartz (1939) found that the workers of several plants in which tar and pitch were handled (manufacturers of electric conduits, roofing paper factories, and tar distilleries) frequently suffered from tar dermatitis and melanosis as well as keratoses and papillomas. However, the two cases of cutaneous malignancies observed by these investigators among the examined tar-workers were attributed to causes other than tar and pitch. This conclusion appears rather unlikely considering the reportedly high incidence of precancerous cutaneous lesions caused by contact with tar and pitch among the workers studied.

No claim is made that the data regarding the incidence of tar and pitch cancer following an industrial exposure are complete; but they are sufficiently comprehensive to permit approximate comparisons as to the relative frequency of these neoplasms in different countries and continents. It is evident that the number of tar and pitch cancers observed in these various regions depends to some extent upon the size and diversity of the industrial establishments producing and handling tar, pitch, and related compounds.

However, the conditions existing in England and Wales indicate, that apart from this factor connected with the regional distribution and size of tar industries, there must be present in these countries a special, predisposing factor, which is probably related in part to the chemical character of the coal used for the production of tar and pitch. It may be attributed in part to the use of ineffective technical and sanitary precautions and of production methods different from those employed in some continental countries. The combination of these factors may account for the marked prevalence of this industrial neoplastic disease in the British Isles. Some credit may also be given to the existence of governmental supervision and obligatory notification of these cutaneous lesions to the Home Office (in force since 1920), since these measures may have added to a more frequent recognition of the high incidence of these tumors observed in England.

On the other hand, the data from some continental European countries are somewhat doubtful as to reliability and completeness. It is clear, that no country has data available, especially preceding 1925, which reflect even approximately the actual incidence of these tumors among the working population. When Pedley asserts that tar and pitch cancer is more common in England and on the European continent than in North America, it must be noted that this statement is correct concerning England, but not continental

Europe, as the United States compares well with the continental countries in regard to tar cancer incidence. Pedley's conclusions, i.e. that the occurrence of tar cancer is by no means confined to the older countries, but also exists in America and that it is only necessary to look to find cases on this side of the Atlantic, deserves increased emphasis.

III. EXPOSURE AND INCIDENCE

Occupational contact with tar and pitch, possibly exciting carcinogenic responses in the exposed individuals, exists in a great number and variety of industrial pursuits:

1) Operations connected with the production of tar (gas-works, coke-ovens, petroleum distilleries, and shale and lignite distillation plants).
2) Factories engaged in the fractionation of tar and in the production of pitch and asphalt.
3) Establishments employing tar, pitch or asphalt for the manufacturing of numerous products of diverse types or using materials containing these substances in a pure or mixed form.

The hazard present in tar-producing plants involves mainly: (*a*) the attendants of retorts, generators, and stills; (*b*) the stokers; (*c*) the workers engaged in the cleaning of these vessels and of the pipes which convey gases, vapors, and fumes to the collecting tanks where tar collects in the cooler parts by condensation. Added to these men who are directly exposed there are those employees who come in contact with tar, as the workers who clean the retorts, soil their hands and clothes with this material and are apt to transfer it to other parts of the plant (handles of covers, doors, and banisters of staircases). The stokers are mainly exposed to tar fumes escaping from the poke hole, while attending to the burning coal in the generator. The danger of contact with tar is more marked with horizontal retorts than with vertical or oblique ones, into which the coal is fed continuously.

The degree of hazard is not only determined by the presence and intensity of exposure to tar, but also by the manner in which precautionary and preventive measures are applied and observed in individual plants. The actual contact may be lessened considerably, if the tar soiling hands, clothing, and parts of the plant equipment is frequently and thoroughly removed (removal of tar from skin with benzol, wearing of gloves and aprons for the protection of clothing and the reduction of contact, daily baths, and special and frequently changed working clothes). According to the observations made by Brenner and Teutschlaender in Germany, Nagayo and Kinosita in Japan, and Wood and Heller in the United States, the actual danger as to the acquisition of tar cancer by the workers in modern gas plants seems to be relatively small. The occurrence of tar cancer of the skin in gas works' employees has been reported by Carozzi; Blum and Bralez; Millian and Garnier; Bang; Stöhr; Lazzarini; O'Donovan; Kennaway; and others.

Similar hazards as to contact with tar exist in connection with the operation of coke ovens. Here the stokers are particularly exposed, as hot tar is apt to splash from the top of the coke oven through the charging holes. There is some danger connected with the pumpmen and workers operating the hydraulic seals and separator tanks, as well as the men cleaning the tar tanks and tar tank cars or loading and unloading tank cars. Tar cancers of this origin have been recorded by Leymann.

Exposure to tar under similar technical conditions prevails during the distillation of lignite and has caused in a few instances cancer of the skin (von Volkmann; Lanfranco).

The conditions existing in tar distilleries are more favorable to an occupational contact with a tar and pitch of marked carcinogenic potency than those found in gas works, as the tar is heated during the process of distillation to high temperatures which enhance the chances of a production of carcinogenic polycyclic hydrocarbons. Some of the workers employed in the older-type factories are engaged in the breaking-up, loading, and removal of the pitch produced, and are exposed during this work to a marked and intimate contact with a carcinogenic pitch dust. In modern plants this hazard is eliminated by pouring the hot liquid directly into tank cars supplied with heating devices, so that the pitch can be reliquified without difficulty at the place of its consumption and can be discharged without any handling (Teutschlaender, Wood). Nevertheless, an appreciable number of precancerous and cancerous cutaneous lesions have been observed in workers employed in pitch plants (O'Donovan; Brenner; Carozzi; Bettazzi; Ball; Nicolas, Lacassagne and Rousset; Oppenheim; Heller).

An important source of occupational contact with carcinogenic tar and pitch exists in the manufacture of patent fuel. The pitch is brought to the older factories in open railroad cars from which it is unloaded by hand into the pitch hole which resembles an open yard. It is sometimes necessary before unloading to chop the pitch which has been exposed, while in transit, to intense solar irradiation causing the melting of the pitch clumps. It is shovelled from the pitch hole, when needed, into carts and brought to the pulverizing machine to be ground. Then powdered pitch is added to coal dust in mixing machines, and by the application of heat and pressure the mixture is finally shaped into bricks or eggs. The finished briquettes are transported back to the yard for cooling and are ultimately loaded on railroad cars, trucks, barges, and other means of transportation.

There is a great deal of dust produced during the breaking, shovelling, piling, wheeling, and grinding operations; it is, therefore, natural that the pitch-breakers, wheelers, shovellers, pilers, and grinders, who have the most intimate contact with pitch dust, exhibit the greatest tendency toward the development of cutaneous pitch cancers (up to 40 per cent, according to

Teutschlaender, when taken as a group; up to 100 per cent, according to Sladden, after being exposed for more than 40 years). The workers employed on the mixers, heaters, and presses (mixers, heatermen, pressmen) are less exposed, because most of these operations are carried out in closed systems, mainly permitting only contact with pitch fumes and steam. They show, therefore, a minor liability to pitch cancer. An appreciable degree of exposure is present, on the other hand, for the individuals (fuel stowers, rope runners, hostlers, coal tippers, and other laborers working in the yards of briquette plants) who handle the finished briquettes. This pertains especially to the loaders of the brick briquettes (the egg briquettes are loaded with a mechanical conveyer), as the bricks contain approximately 7 per cent pitch. A similar exposure exists for the men handling the patent fuel during its consumption, such as stokers and firemen of railroad engines and ship's boilers.

In modern briquette plants in which either the Fohr-Kleinschmidt or a similar method of production is used, the dust hazard is almost completely eliminated (Grempe; Teutschlaender; Heller). The first installation of this method was made in Germany in 1912-1913 (Teutschlaender) at Engelsburg near Bochum. The technical advantage of this method is the use of liquid pitch which permits a more efficient, uniform, and economical mixture of the powdered coal (brown coal or anthracite) with the binder. The freshly-produced hot pitch is loaded into special tank cars at the place of production (usually coke oven plants), and is brought in this hot, liquid state directly to the patent fuel plant, where it is pumped from the tank car and sprayed into the mixing drum filled with coal dust. Since the entire operation is automatic and takes place in a closed system a distinct saving of labor is obtained, and simultaneously, altho originally unintended, a marked diminution of the occupational exposure to pitch dust ensues. Plants working on this or a similar system have been erected later in many parts of Germany as well as in the United States (Teutschlaender; Wood). Not a single case of pitch cancer has been observed among the workers employed in a German plant operating on this system since 1914 (Teutschlaender). Similar observations were reported by Wood concerning the occurrence of pitch cancer among American patent fuel workers. The binder used in the manufacture of American briquettes is not coal tar pitch usually, as is used in Europe, but petroleum asphalt (Heller), a substance of lower carcinogenic potency.

Cancers in briquette plant workers have been placed on record by Leymann; Bering and Zitzke; Teutschlaender; Fuss; Leclercq and Cordonnier; Jaqué and Sluys; Müller; de Vries; Sladden; Bridge and Henry; O'Donovan; Eisner; Manouvriez; Legge; Wignall; Downing; Kranenburg. Teutschlaender and Leymann mentioned the occurrence of pitch cancer among railroad stokers who handle brick briquettes.

The incidence rate of pitch cancer among patent fuel workers can be appre-

ciated properly, if consideration is given to the fact that actually only 8 to 10 per cent of the men employed in such operations are markedly exposed to this agent (Teutschlaender). The statement of Leymann that 10 cases of pitch cancer, in addition to numerous precancerous pitch warts, had been recorded among 2,500 men working in 65 hard coal briquette plants in Prussia, must be evaluated in the light of this information. Downing listed the following incidence of pitch papilloma and cancer among the various groups of patent fuel workers:

Occupation	Number of Papillomas	Number of Men Employed
Heatermen	11	9
Pitch Wheelers	23	54
Loaders and Fuel Stowers	20	36
Laborers and Tippers	7	35
Ovenmen	5	7
Millmen, Grinders	3	18
Block Regulators	1	4
Pressmen	1	6
Roperunners	1	3
Hostlers	1	2
Total	73	174

The incidence of pitch papillomas is greatest, according to Downing, among heatermen, pitch wheelers and fuel stowers. Downing declared that small traumatic injuries produced by flying pieces of pitch as well as marked perspiration induced by the handling of hot briquettes (pitch being soluble in sweat) intensified the action of pitch and aided in the development of the neoplastic response.

Sladden (1928) reported that in the Swansea district, where about 900 men are employed in the patent fuel industry, there were 13 cases of epitheliomas in 1920 and 1925, while 5 cases per year were found on the average during the intervening 4 years. Commenting on these figures, Sladden emphasized the fact that the incidence of pitch cancer in the various briquette plants depended upon several factors and, thus, was not uniform. Factors influencing the cancer rate are, according to Sladden, number and age of men employed, duration of employment, continuity of exposure, degree of exposure, character of pitch used, degree of attention paid to preventive and precautionary technical as well as sanitary measures, and periodical medical examinations. Sladden found among 200 patent fuel workers, 150 of whom came for their routine medical examination, while 50 came to the hospital because of some skin lesion, evidence of pitch skin in 50 per cent of the first

group, the incidence of this condition increasing with the age of the individuals and the years of employment. Kranenburg observed in 1929 among 243 Dutch workers of briquette plants one case of pitch cancer and 136 cases of pitch warts. The data presented indicate that the briquette industry has remained, even during recent years, in some countries an important source of industrial pitch cancer of the skin.

Manufacturers of building material and men engaged in the building trade represent another occupational group which may be exposed to pitch and tar and consequently become affected by tar and pitch epithelioma. Such a carcinogenic hazard exists for the producers and users of weather-proof stones which are made by compressing a mixture of tar, pitch, and gravel into the shape of bricks. These are dipped into liquid tar to provide them with a coating of tar. The preparation and use of water-proof concrete, made by mixing cement with pitch and tar, as well as the painting of foundations and outside walls of buildings with tar or pitch are connected with similar dangers (Haagensen).

However, the most serious situation in this respect is in the manufacturing and use of corkstone, which has become an important building material in modern construction. Corkstones are made of ground cork waste to which various ingredients are added as binders, the nature of which depends upon the future use of the corkstones and plates. While the greyish-white corkstones contain clay and lime as a binder, pitch is used in the manufacture of the water-proof corkstones.

The main exposure to pitch occurs, first of all, before this substance is mixed with the powdered cork, and later on, in the processing and handling of the finished material. The group of workers having the most contact are, on the one side, the loaders, breakers, and grinders of pitch, and on the other side, the sawers, lathe workers, and polishers of corkstones, tiles and plates. The hazard is not restricted alone to the manufacturers of corkstone, but, also, extends to the members of the building trades who use the finished material. In both instances the exposure consists of contact with pitch dust in great quantities. As they are very durable, light in weight, elastic, fire-proof, resistant to pressure, and can be handled like ordinary brick or wood, corkstone tiles and plates are widely used for sound-proofing and insulation (temperature control) of walls and pipes, and for floor covering (tiles or under linoleum).

At present there are 17 cases of pitch cancers among corkstone workers, nine of these cases having been observed among workers in several Swiss plants employing a total of 63 workers (incidence of 15 per cent). The incidence is relatively higher (20 per cent) when only workers appreciably exposed to pitch dust are considered. When individuals of 50 years or more are considered the incidence increases to 31 per cent (Schürch; Schürch and Schrafl; Barkmeyer). One case from a Hungarian corkstone factory was reported by

Doleschall, and seven cases from a German plant were recorded by Lauchs. The occurrence of pitch cancer among workers of this occupational group was, also, mentioned by Hope; and Chorodov and Spector.

An additional source of pitch cancer was discovered by Heller in a carbon factory in Cleveland, where calcined carbon flower (a mixture of lamp black and coke) was softened by the addition of light tar oil and, then, mixed with a medium tar pitch for a binder. The mixers were exposed to pitch fumes and dust, while the millers engaged in grinding operations were exposed mainly to pitch dust. Until 1915 the carbon plates were moulded by hand. After this date the operation was done by hydraulic forming machines, so that only the men shovelling and loading pitch into the melting kettles had any appreciable contact with pitch dust. Between 1920 and 1930 twenty-one cases of skin cancer occurred among the workers, in spite of the installation in 1915 of an exhaust ventilation used to combat the dust hazards.

The manufacture of roofing paper represents another source of pitch-tar-asphalt cancer of the skin. Tar paper is made by soaking paper in tar and drawing this paper through rollers heated to 240°F. In the course of this work the hands and arms of the laborers become soiled with tar. In 1910 Schamberg examined twenty-one workers employed in this field and found 5 of them affected with beginning or well-developed epitheliomas. In 1885 Ball reported two cases of skin cancer from two similar plants employing 17 to 19 men; while Lennhoff and Haagensen mentioned the occurrence of skin cancer in roofers using tar paper as well as paint with tar or mixtures of tar with pitch and asphalt. Similar hazards and results have been observed in connection with the manufacture of felt impregnated with tar and of insulation paper made by the impregnation of paper with asphalt (Nuck).

Tar and pitch cancer has been observed among workers employed in the construction and maintenance of roads (Oliver; O'Donovan; Hunt; Lehmann; Haagensen; Baader), tar cookers, mixers, sprayers, and road menders being those mainly affected.

The extensive use of tar, pitch, and asphalt in the shipbuilding and fishing trades has given rise to a considerable number of skin epitheliomas (Bristol; Shambaugh; etc.) among shipbuilders, fishermen and sailors. Tar and pitch are used for closing seams in ships and boats by calking them with a material containing hemp and tar or asphalt. Tar, asphalt, and pitch are used for the impregnation of nets, ropes, cables, tarpaulins, poles, and deck-floors.

The use of tar or asphalt in providing a protective lacquer for iron pipes (Henry; David-Brassart) and for the lining of Bessemer-Thomas converters (Baader; Beintker) has led to the occasional development of skin cancer among the exposed workers.

Precancerous and cancerous cutaneous lesions have been seen in workers engaged in the production of coal grease, which is made by mixing hot tar oil with small quantities of lime and resin, and, also, in men using the finished

material (Legge; Oliver; Schärer; Habermann; Hoffmann; Barnewitz).

The use of tar, pitch, and asphalt in the electrotechnical industry and in the manufacture of electrical appliances has led to an appreciable number of dermatoses and a few epitheliomas among the workers employed in such operations [insulation tape, dry battery cases, electrical cables, insulation of electrical appliances (molders, mixers, seal makers), and electrode pressing] (Baader; Betke; Büngeler; Arnstein; Heller; Carozzi; Foerster and Schwartz; Barkmeyer; Raabs).

The occurrence of a pitch dermatosis in cobblers using pitch for the impregnation of sewing thread has been noted by Oppenheim and Lutz; while Stahr reported a cancer of the thumb of a cobbler's apprentice who had frequently punctured the skin with the point of his awl.

The use of pitch as one of the ingredients (colophonium) of a lubricant, employed by glass blowers for greasing the palms of their hands when they rotate the hot iron blow pipe, has been recorded by Oppenheim; Epstein; Glaser; and Stein. Epstein, also, reported the development of a cancer in the palm of the left hand of a glass blower thus exposed.

The recorded occurrence of skin cancer in brush makers using wood tar (Bridge and Henry) should be mentioned as well as that in a hemp rope maker who employed the same material as a lubricant and for impregnation (Weiss).

Lauchs and Neumann noted the occurrence of skin cancer in workers using wood tar in the manufacture of wire cables; and Veiel observed a case following a prolonged therapeutic application of pinene tar.

From an analysis of the great number of communications dealing with the effects of an occupational contact of tar, pitch, and asphalt upon the skin of male and female workers, the remarkable conclusion must be drawn, that the development of non-neoplastic, and often precancerous reactions, is a very frequent phenomenon; while cancerous responses are relatively rarely observed in the majority of industries in which such a hazard exists. However, a much greater amount of extensive and reliable evidence is needed before this conclusion can be accepted as definite.

The following types of tar, pitch, and asphalt have been incriminated in the production of industrial cancer of the skin: gas works tar, producer-gas tar, coke-oven tar (Kennaway; Baader; Leymann), shale oil tar, lignite tar, anthracite-retort tar (Leymann; Rambousek; Zweig), blast-furnace tar [for mice (Berenblum, 1930; Bonser; 1932); not for man (Legge; Kennaway); and, not for mice (Leitch, 1923)], gas-tar pitch, coke-oven pitch, certain petroleum asphalts, and certain wood tars (pinene) (Weiss; Neumann; Bridge and Henry; Twort and Fulton; Veiel; Watson; Kotzareff and de Morsier). Water-gas tar is said to be noncarcinogenic (Wood). Kennaway demonstrated the carcinogenicity of certain synthetic tars prepared by passing isoprene and acetylene through tubes heated at 700°-900°C. These synthetic tars are of

special importance from a chemical and etiological standpoint as they contain only carbon and hydrogen, and no oxygen, nitrogen, and sulfur which are present in coal tar. Tar made at high temperatures by the distillation of cholesterol, bone, human tissue, yeast, rice bran, and tobacco was shown to be carcinogenic for mice (Kennaway; Roffo).

The controversial aspect of the carcinogenicity of blast-furnace tar was commented upon by Bonser who proposed the following explanations for the absence of neoplastic skin lesions among iron workers tending blast furnaces: although blast-furnace tar possesses the character of a low temperature distillation tar, the high oxygen content of the Scottish splint coal causes the production of a large amount of phenolic compounds; the total yield of blast-furnace tar, which contains a relatively large amount of water, is low; the small amounts of blast-furnace tar produced are handled differently than in gas works, as the tar represents a waste product, which is immediately disposed of; and the carcinogenic potency of blast furnace tar is low.

IV. SYMPTOMATOLOGY

Tar, pitch, and asphalt, while representing a varying mixture of diverse hydrocarbons, produce, nevertheless, a cutaneous syndrome which is relatively uniform in character and sequence of manifestations, wherever they occur. The site of the non-neoplastic, preneoplastic, and neoplastic lesions differs with the type of the occupational activity and the mode of contact with the agents mentioned above. The various cutaneous reactions elicited by tar and pitch can be divided into three main groups: (*1*) Inflammatory responses resulting primarily from a chemical and photo-chemical irritation (erythema, dermatitis, folliculitis); (*2*) pigmentary disturbances of the skin (melanosis) caused by an accumulation of endogenous and exogenous brown pigmentary matter in the skin; (*3*) hyperplastic and neoplastic (benign and malignant), proliferative manifestations. Generally, the first two types of cutaneous changes precede those of the proliferative variety and usually continue to co-exist with them. They possess the character of occupational stigmata, and, also, the warning signs of potential future reactions of more serious nature. While these non-neoplastic lesions persist for a long time and accompany in most instances the appearance of the blastomatous manifestations, occasionally they recede before the neoplasms develop. This happens only when the epitheliomas follow many years after the cessation of exposure to tar or pitch. Thus, the absence of the preliminary inflammatory and pigmentary disturbances at the time of the neoplastic development does not exclude the occupational origin of these manifestations.

The primary acute reaction which develops after the first cutaneous contact with tar or pitch consists of an intense erythroderma, often associated with conjunctivitis, lacrimation, and photophobia. The exposed workers experience tenseness and smarting pains combined with itching in the affected parts of

the skin, especially when subjected to direct and intense solar irradiation. The painful, burning sensations are exaggerated when they attempt to wash the tarry grime with soap and warm water. Consequently, tar and pitch workers soon develop an intense dislike for washing and bathing, particularly of those parts which are either most exposed to tar and pitch, or which are especially sensitive to their action because of the macerating influence exerted upon the skin by the normally marked perspiration, such as the skin of the face, neck, and the external genital region. After a few days of this initial reaction the skin starts to crack and may desquamate in shreds. These early manifestations are occasionally so severe that some workers are forced to relinquish their jobs. Although the acute symptoms in the majority of workers subside after a while and are replaced gradually by reactions of a more chronic nature, there still remains the hypersensitivity of the skin to light and wind. This condition explains why tar and pitch workers prefer to work in darkened rooms and pass their free time in shady, cool quarters.

With the fading of the hyperemic red color, the skin assumes an increasingly brown discoloration which may show lighter yellow or grey tints depending, in part upon the intensity of contact, and in part upon the type of tar or pitch exposed to. Not infrequently pitch workers have a brownish-black to greenish-black color of the face and neck, especially of the back of the neck, the nose, and lower eyelids. Often the external genitals are darkly pigmented. This bronzing of the skin, also, develops after an exposure to tar or pitch fumes. As the cutaneous capillaries of the face, especially of the cheeks, become telangiectatic and congested in many instances, the brownish color may assume a reddish hue giving the individual a dusky or swarthy complexion. The melanosis of the involved parts of the skin is not uniform. A close inspection reveals mottled, pitted, ring-shaped, and perifollicular accumulations of pigment often merging into a network-like pattern. Usually, the spotty character of the melanosis is particularly pronounced on the hands and forearms; and the brownish discoloration forms upon the white of the sclera, being limited, however, to the region of the lid slit.

In addition to the melanotic changes of the skin, eczematous lesions, acneiform efflorescences and folliculitis develop during this stage. The latter manifestations are particularly frequent whenever the occupational activity entails an intense exposure to tar or pitch dust, which clogs the follicular openings and causes the development of numerous comedones. These may occur either from chemical irritation of the hair roots, or from secondary bacterial infection which causes multiple inflamed follicles or furuncles. These affect the scrotal sac, the anterior surface of the thigh, forearms, and, occasionally, the face and posterior aspect of the neck.

None of these inflammatory responses and pigmentary disturbances have ever developed into a neoplastic lesion. They are capable of active spontaneous regression. Only the comedones may persist for an extended period. Conse-

quently, after several months without contact with tar or pitch the skin of a tar or pitch worker may assume a somewhat normal color and appearance (Koelsch; Chorodov and Spektor; Müller; Foerster and Schwartz).

With the progressive development of a chronic tar and pitch dermatitis the skin becomes dry, scaly, studded with small papules, rough, and harsh like shagreen. As the papules itch, the workers develop the habit of removing the thickened epithelium by scratching. In this way the follicular openings underneath become filled with black tar or pitch. The small, black-topped keratoses thus formed vary in size from a pin head to a split pea.

These epidermal, keratotic thickenings are the first evidences of proliferative manifestations which, from then on, may make their appearance in various forms. Pedunculated, papillomatous lesions occur next. These lesions have either the morphological character of cutaneous horns, or villous, papillary projections with slender, delicate stems varying in length from 0.2 to 0.5 cm. and possessing, like the horns, dark-brown tips. These so-called "dry warts" bleed easily and may persist for a long time without undergoing any further changes. Some of them undergo spontaneous, regressive alterations and finally drop off; others are either rubbed off by the workers with a rough towel, removed by repeated applications of a moistened soda crystal or acetic acid, or by tearing. A small, round scar remains from these warts, which are most frequently located on the eyelids, and around the nose. Because of their customary benign behavior and the absence of recurrences, these pedunculated papillomatous warts are considered by the workers as trivial lesions.

The second type of neoplastic reaction makes its appearance as an intraepidermal papule, which can often be detected by palpation before it becomes visible as a hard, protruding, keratinized nodule possessing a broad base and a smooth surface. Later on the papule may assume the form of a sessile, papillomatous wart ("wet wart"), or it may acquire a conical umbilification with a black center. The sessile, flat papillomas occur both singly and in groups, and are the more common lesions. While they may regress spontaneously, some undergo superficial degeneration resulting in a serous exudation and a crust formation. If the crust is removed by force, the bare surface bleeds freely. Ultimately, there develops an ulceration, which usually involves the apex of the papillomatous wart, and which is evidence of its malignant transformation. The cancerous development of the conical depression is preceded by the disappearance of the keratinized center and the appearance of a crusty crater. After remaining in this stage for 2 or 3 months or longer, this precancerous lesion ulcerates and assumes malignant qualities. Following the malignant transformation, which is occasionally precipitated by a trauma (Sladden), the edges of the ulcers become elevated and indurated, and a sanguinous exudate is discharged from the malignant lesion. The degree of proliferative activity exhibited by these cancers depends to some extent upon their location. They do not grow rapidly when on the face or on the forearms,

but they display an appreciable local spread and a relatively quick extension into the regional (inguinal) lymph nodes when the scrotal sac (where they generally involve the anterior aspect) is affected (Sladden; Downing; Ullmann; Teutschlaender; Schürch; Lauchs; White; Oppenheim; Koelsch; Legge; Hoffmann and Habermann; Schärer; Arnstein; Wieder; Eisner; Ehrmann). Sladden noted that the warts which often appear in large numbers on the skin of the arms show a minor tendency to become malignant. Similarly, those parts of the skin, which are the most common sites of the benign pitch warts, do not necessarily exhibit the highest liability to malignant lesions.

V. SITE

Warts are commonly found on the exposed parts of the skin (face, scalp, neck, hands, and forearms) and on the scrotum of men working with tar, pitch, and asphalt. The malignant lesions occupy similar sites. The relative, local distribution of these neoplasms differs within the various occupational groups, as it depends upon different types of occupational activity and the thereby conditioned contact with cancerigenic agents.

The great majority of tar workers (workers in gas-plants, tar distilleries, roofing paper and felt factories, road workers, and tar painters) contact tar by handling the substance itself, materials soiled with it, or by having liquid and, often hot tar accidentally splashed upon the exposed parts (hands, forearms, and face) or their clothes. From these chief locations tar may be transferred secondarily to other parts of the body. The penetration of tar in tar-soaked clothes or the handling of the penis with soiled fingers may result in an exposure of the penis and the scrotal sac to tar.

While the haired parts of the head are rarely affected by tar cancer, the regions covered by beards seem to represent an apparent exception. This is because of the habit that tar workers have of touching and rubbing their beards with their tar-soiled hands. The following table lists sites and local distribution

Sites of Tar Epitheliomas

Head and Neck	63	Upper Limb	61	Genital Region	34	Other parts	0
Forehead	1	Forearm	21	Scrotum	32		
Face	19	Wrist	11	Penis	1		
Nose	9	Hand	28	Groin	1		
Eye & Eyelid	10	Thumb	1				
Nostrils	2						
Cheeks	9						
Lips	5						
External Ears	6						
Neck	2						
Bridge and Henry	58		38		92		13

of 158 tar epitheliomas observed in 148 recorded cases (including the compilations of Kennaway; Heller; and Legge), while a similar analysis, added for comparison and as a supplement (Bridge and Henry), gives a regional grouping of 201 cases of tar cancer.

A plausible explanation cannot be offered for the marked discrepancy, between the two compilations, in the numerical distribution of tar cancers upon the four regional groups. Differences in the occupational sources, from which the statistical data were taken, may account for the prevalance of the scrotal cancers in the tabulation of Bridge and Henry. Kennaway stated that tar cancers are, approximately, equally distributed among the first three regions listed (head and neck; arm and hand; scrotum).

The occupational exposure to pitch is mainly one to pitch dust. Proliferative reactions may be expected to occur in regions where direct contact is the greatest, where pitch dust is most readily retained in skin folds and rugosities, and where additional functional and anatomical peculiarities of the skin may increase the physical and chemical action of pitch upon and into the skin. It is for these reasons that pitch cancers show a local distribution which is somewhat different from that for tar cancers. The site of pitch tumors, observed in several occupations, reflects the mode of contact peculiar to different occupational activities (glass blowers: palms of hands; cobblers: thumbs; electric workers: fingers).

The following table presents the local distribution of 363 pitch papillomas (Sladden; Teutchlaender; and Downing).

Sites of Pitch Papillomas

Head and Neck	275	Upper Limb	55	Genital Region	28	Other Parts	6
Forehead	7	Forearm	36	Scrotum	25	Trunk	5
Face	49	Hands	19	Penis	1	Chest	1
Nose	51			Thigh	2		
Eye & Eyelid	51						
Cheek	20						
Chin	2						
Lips	43						
Scalp	3						
Ear	22						
Neck	27						

The local distribution of precancerous lesions exhibits the marked predominance of the head and neck as regions most frequently affected. This observation is important in view of the local distribution of the 486 recorded pitch epitheliomas, including the compilations of Legge; Kennaway; Sladden; Downing; Teutschlaender; Schürch; Barkmeyer; and Lauchs. A tabulation of 163 pitch cancers according to their distribution upon the four regions reported by Bridge and Henry is presented for comparison.

Sites of Pitch Epitheliomas

Head and Neck	154	Upper Limb	32	Genital Region	120	Other Parts	4
Forehead	1	Forearm	13	Scrotum	116	Chest	1
Face	18	Wrist	2	Penis	4	Back	1
Nose	10	Hand	15			Leg	2
Eye & Eyelid	31	Finger	2				
Cheek	26						
Chin	6						
Lips	40						
Scalp	3						
Neck	8						
Ear	11						
Bridge and Henry	116		11		28		8

While pitch papillomas follow tar cancers in regard to their local distribution, showing a prevalence for head and neck lesions, pitch epitheliomas exhibit a marked tendency for localizing on the scrotal skin, similar to chimney sweep's cancers and epitheliomas seen on mule spinners. This conclusion, reached through data obtained from numerous sources, is neither in agreement with the statistical evidence supplied by Bridge and Henry, nor supported by the observations of Kennaway. This investigator stated that pitch is more liable to cause cancer of the head and neck than of the scrotum (63 cancers of the head and neck against 32 epitheliomas of the scrotum). It was asserted, moreover, by Kennaway that neither the rugosity of the scrotal skin nor its abundance of sebaceous glands, and thus a marked production of sebum, produce any predisposition for pitch cancer. These contentions, however, are of controversial nature. Sladden, for instance, maintained that sebum favors the absorption of carcinogenic material, while White acknowledged this rôle of sebum only when it is present in excess. Downing claimed that sebum was a protective against the action of pitch and tar. This assertion agrees with the observation that colored persons (Negroes), who normally have oily skin, appear to be much less susceptible to pitch and tar cancer than white persons, especially those having dry skin.

There exist, however, a number of additional factors which favor the development of pitch cancer in the scrotal skin. Although the duration and intensity of exposure to any carcinogenic agent plays a rôle concerning the causation and onset of the neoplastic response, it is certain that the rugose character of the scrotal skin, which favors the retention of pitch, facilitates the cancerigenic action of this agent. An abundant sebum production helps in fixing the pitch dust to the skin, and in hindering its ready removal by soap and water, which is, also, interfered with by the rugosities. Apart from the presence of the carcinogenic agent these accessory factors may be added:

the relative inaccessibility of the scrotal skin to a thorough cleansing, the discomfort experienced during such a procedure, the diffidence among workers in submitting to medical examinations of the scrotum, and the friction of clothing against the scrotum (Sladden). Some of these considerations are advanced to explain the occurrence of pitch cancers in other regions of the body, such as the dorsum of the penis and the nape of the neck (friction by collar) (Downing).

VI. MULTIPLICITY

Multiplicity of proliferative, reactive, cutaneous manifestations following occupational contact with pitch and tar is a common feature of hyperplastic and benign neoplastic, papillomatous lesions, but it is less frequent in cancerous responses. Benign warts are more often than not multiple, and may involve simultaneously various and widely-separated parts of the skin (such as the face and scrotum, or the forearms and neck), or they may be found on all exposed parts of the skin and on the penis and scrotum (Sladden; Bering and Zitzke; Schürch and Schrafl; Downing; Lauchs; Fuss; Schamberg; Jaqué and Sluys; DeVries; Barkmeyer; Goulden and Stallard; Oliver; Müller; Eisner). Sladden observed multiple pitch warts in 125 cases out of 200 studied. These benign, epithelial excrescences occur not only as precursors of malignant proliferations, preceding them by up to 25 years (O'Donovan), but are also found in co-existence with pitch cancers.

The multiplicity of tar and pitch cancers is partly of a simultaneous character and partly of a successive type, with several years intervening between the appearance of individual carcinomas. Similar to the local distribution of benign warts, the cancers may affect widely separated parts of the skin and even involve heterogenic, i.e., internal organs, such as the urinary bladder (Sladden). Multiplicity of tar and pitch cancer is related to the time of exposure and is generally found in individuals, 41 to 50 years old (Downing).

Kennaway observed multiple tar and pitch cancers of the scrotum in 7 cases out of 33; in 3 instances there were 3 primary cancers, and in 4 instances 2 cancers co-existed. Downing noted a multiplicity of pitch cancers in 16 cases out of 76. Additional reports of multiple tar and pitch cancers were made by Sladden; Bering and Zitzke; Schürch and Schrafl; Barkmeyer; Goyanes; and Eisner. In addition to the scrotum in the seven cases recorded by Kennaway, the following organs were affected: penis, twice; eye, once, neck, once; nose, once; chin and leg, once; and face, once. In two additional cases observed by Kennaway multiple pitch cancers affected, in one case, the lip, face, and hand, and, in the second case, the arm, leg, and cheek. Barkemeyer mentioned a case of multiple pitch cancer in a corkstone worker, who was first affected by two cancers, one located on the scrotum and one on the penis. Later, another cancer appeared on the penis, while still later three additional, malignant epitheliomas developed on the exposed parts of the skin. In a second case of

multiple pitch cancer, described by the same investigator, a corkstone worker first showed a cancer on the corner of the eye, followed by a cancer on the lower lid, which, in turn, was succeeded by an epithelioma on the other eyelid. Sladden mentioned a case of multiple pitch cancer, in which the first tumor was situated on the external ear, while the second involved the scrotum. The same investigator related a case of heterogenic, multiple, malignant responses which developed in a pitch worker, affecting successively scrotum, jaw, lip and, ultimately, the urinary bladder. A case of successive multiplicity of pitch epithelioma in a corkstone worker affecting successively lip, nostrils (3 cancers), forehead, and corner of the eye was reported by Lauchs. Brenner found in a laborer in a tar distillery, first, a cancer of the ear, which was later followed by an epithelioma of the cheek. Multiple pitch and tar cancers are not uncommon, according to these observations, which contradict Sladden's contention that pitch cancers are and usually remain solitary new growths.

VII. PROGNOSIS

The ultimate prognosis of tar and pitch cancer is determined by various factors. It is obvious that the diffusiveness of skin changes, existing in the majority of the affected workers, favors the occurrence of successive primary tumors, and influences the ultimate prognosis although the first malignancy is successfully removed. This course and prospect is made more definite, if the tar or pitch worker affected by a cutaneous malignancy continues his occupation. The ultimate prognosis is made markedly worse by such a combination of anatomical and occupational conditions (Teutschlaender; and Schürch).

Furthermore, the prognosis depends, apart from the extent of the primary tumor at the time therapeutic procedures are instituted, on the site of the neoplasm. Cancers situated at the scrotum metastasize more readily into the regionary nodes and from there into the internal organs than those located on the face, neck, arms, and hands. In general, the growth rate of pitch and tar epitheliomas is a slow one and metastases occur late in the course of the disease.

English investigators have furnished some data from which relative prospects of tar and pitch malignancy in regard to the actual danger to life may be gauged. Legge reported that out of 66 cases of pitch cancer notified during 1920 to 1922 two ended in death, and the same number of fatalities was observed during this period among 21 cases of tar malignancy. Bridge and Henry supplied for the years 1920 to 1927, and 1933 to 1937, the following data:

Pitch operations:	163 cases of epithelioma	5 deaths	1920-1927
	146	5	1933-1937
Tar distilleries:	103 cases of epithelioma	13 deaths	1920-1927
	238	13	1933-1937

Gas Works:	55 cases of epithelioma	21 deaths	1920-1927
	75	38	1933-1937
Other Industries:	46 cases of epithelioma	6 deaths	1920-1927
	35	7	1933-1937

Including the cases which occurred during the year 1929, the percentage of fatalities from tar and pitch cancer among English workers affected by this disease presents itself as follows: pitch cancer: 336 cases with 11 deaths; tar cancer: 602 cases with 112 deaths.

This compilation brings out the interesting fact that tar cancer offers a much worse prognosis than pitch epithelioma. At the present time a plausible explanation for this phenomenon cannot be offered. The possibility exists that the physico-chemical properties of tar enable a better and deeper penetration of the carcinogenic agent into the cellular layers of the skin, than those of pitch, occurring mainly in the form of dust. As this observation is based entirely on English data, consideration must be given to the fact that tar apparently produces scrotal malignancy more often among English workers (Bridge and Henry) than among continental workers. This fact may account in part for the bad prognosis of tar cancer in England.

VIII. AGE

It has been maintained by various observers that advanced age represents an intrinsic, predisposing factor for development of cancer of the skin in individuals exposed to tar and pitch (Teutschlaender). They have, therefore, warned, against the employment of such individuals in tar and pitch operations. Other investigators have maintained that duration of exposure rather than absolute age, that is, a hypothetical tissue senility, plays the chief role in the production of tar and pitch malignancy (Kennaway). The following tables illustrate the age distribution of pitch papillomas, pitch cancer, and tar cancer as it is presented by a survey of data available.

AGE DISTRIBUTION OF PITCH WARTS (Downing)

Years	21–30	31–40	41–50	51–60	61–70	Total
Cases	4	9	24	16	8	61

AGE DISTRIBUTION OF PITCH AND TAR EPITHELIOMAS

Years	15–19	20–29	30–39	40–49	50–59	60–69	70–79	80 and more	Total
Pitch Cases	1	5	14	34	38	20	3		115
Tar Cases			6	14	15	32	12	1	80

These compilations show (1) that pitch papillomas occur, in general, at an earlier age than malignant sequelae, (2) that pitch epitheliomas, while affecting occasionally relatively young individuals, are most commonly found in persons being in their fifth and sixth decade. In contrast, tar cancers show a high frequency peak during the seventh decade. This discrepancy in age distribution between pitch and tar malignancies may be caused by two factors, assuming that the initial age of employment of the tar and pitch worker as well as the duration of exposure is the same in both groups. The observation may indicate that pitch is of higher carcinogenic potency than tar, and the degree of exposure to pitch is more intensive than that to tar. Either one or both reasons may be operative in bringing about this discrepancy.

An analysis made by Sladden of the incidence of pitch cancer among briquette workers in relation to their age displays a similar relation as that shown in the table on "Age Distribution of Pitch and Tar Epitheliomas."

Years	15–25	25–30	30–35	35–40	40–45	45–50	50–55	55–60	60 and more	Total
Number of Men Examined	9	16	17	25	19	21	20	17	14	158
% With Warts& Epitheliomas	0	19	18	28	42	33	85	65	72	362

Although the frequency of tar and pitch cancer increases to some extent with the advancement in age, an evaluation of the relation between time of exposure and incidence of tar and pitch carcinoma exhibits the intimate dependence of the latter phenomenon upon the duration of contact with carcinogenic agents.

IX. DURATION OF EXPOSURE

DURATION OF EXPOSURE AND PITCH WARTS (Downing)

Years	1–5	6–10	11–20	21–30	31–40	41–50	Total
Cases	5	7	21	17	8	0	58

DURATION OF EXPOSURE AND PITCH AND TAR CANCER

Years	1–5	6–10	11–15	16–20	21–30	31–40	41 and more	Total
Pitch Cancer	14	30	40	39	78	32	4	237
Tar Cancer	3	18	37	28	63	47	17	216

These compilations bring out the fact that a somewhat shorter duration of exposure to pitch is necessary to elicit an epitheliomatous response than is required by tar. Observations made by Baader; Schürch and Schrafl; and Barkmeyer suggest that, occasionally, only a few years of contact with pitch results in the production of malignancy. Baader saw a cutaneous malignancy in a pitch grinder after 24 months of work; Schürch and Barkmeyer reported the appearance of epitheliomas in corkstone workers after 18 months, 24 months, and 36 months (3 cases) of work, respectively.

The evidence presented suggests that age or physiologic tissue changes connected with the aging process apparently play no or a minor rôle in the genesis or susceptibility to tar and pitch cancer. The occurrence of pitch epitheliomas in several very young adults and the occasional appearance of these neoplastic reactions after a relatively short time of occupational contact point to the existence of individual variations in reactivity to carcinogenic action of tar and pitch.

This conception is supported by an observation made by several investigators (Downing; Koelsch; Lewin; Wieder; Teutschlaender; Lehmann; and Foerster and Schwartz) which indicates that individuals with a fair complexion, blond hair, and blue eyes (persons of German and Irish extraction [Foerster and Schwartz]) are especially susceptible to eczematous as well as cancerous action of these two products. Lewin noted that of 103 pitch workers with cutaneous reactions studied, 89 (86.4 per cent) were blond, while 14 were brunette. Similar observations as to the existence of racial differences in this respect, were recorded by Heller, who found that Negroes show less sensitivity to carcinogenic and eczematogenic action of pitch and tar than white workers. However, investigations of Sladden have shown that such individual differences in sensitivity are overcome sooner or later, and that eventually a malignant cutaneous reaction will ensue in all exposed persons, provided the duration of exposure is sufficiently long and intense.

INFLUENCE OF EXPOSURE UPON SUSCEPTIBILITY TO PITCH CANCER (Sladden)

Years of Exposure	1–5	5–10	10–15	15–20	20–25	25–30	30–35	35–40	40 and more
Total Number Seen	40	38	22	9	13	14	13	5	4
% of Warts and Cancer	17	21	36	67	69	71	77	80	100

X. SEX

The male sex has been mentioned exclusively in connection with the occurrence of occupational tar and pitch tumors. This is mainly because the great

majority of workers, who come in contact industrially with these substances for long periods of time, are of the male sex. However, there are reports available concerning the appearance of non-neoplastic and precancerous manifestations in female workers. Arnstein noted the occurrence of melanoderma of the face, neck, hands, and forearms in seven women, who assembled dry batteries and covered their cases with liquid tar in an ill ventilated room, where they were constantly exposed to fumes from melted tar as well as to direct contact with this substance. Leymann mentioned that women are especially susceptible to tar dermatosis. The apparent absence of occupational tar and pitch cancer among women is probably attributable to two factors: (*1*) As many of them leave the industrial work after becoming married, women workers are not subjected, as a rule, to long, sustained exposure to these substances; and (*2*) As tar and pitch cancers have a long latency period, sometimes becoming manifest many years after pigmentary and inflammatory reactions have subsided and disappeared, their etiology may go unnoticed, unless a detailed inquiry into past occupational history of married women with skin cancer is made.

XI. CONSTITUTION

The rôle, which constitutional factors (color of skin, hair, and eyes, thickness of skin, and functional activity of skin glands) apparently play in connection with individual reactivity to the irritative and carcinogenic action of tar and pitch, has been briefly mentioned before. These factors undoubtedly influence susceptibility to and development time of pitch and tar cancers. Since fair-complexioned individuals have been found to be more sensitive than dark-complexioned persons, tar distilleries in the United States employ, according to Heller, predominantly Negroes in operations having intimate contact with tar and pitch.

XII. LATENCY PERIOD

The data relating to exposure time indicate that tar and pitch cancer require for their causation and development a latency period of many years. They rarely become manifest after an exposure of only a few months or years to these agents. Tar and pitch cancers may delay their appearance for many years (up to 20 or 30 years) after work with tar and pitch stops (Sladden; Downing; O'Donovan). These cases are of special, scientific and medico-legal significance; they raise important questions concerning the type of causative mechanism operative in their delayed development, and they fail to come under the regulations of compensation laws in those countries where a time-limitation clause for claims of such occupational diseases is in force (Downing).

XIII. ACUTE TRAUMATIC TAR CANCER

Contrasting with the well established occurrence of tar and pitch cancers of industrial origin showing a delayed appearance, claims have been advanced concerning the precocious development of tar epitheliomas following a trau-

matic contact with tar (Gunsett; Bang; Huguenin). In two cases of this type reported by Bang and Huguenin, the affected individuals prior to the accidental episode, had been subjected to an extensive and prolonged occupational exposure to tar and mazoute, respectively. The acute, neoplastic response was provoked by accidental burns caused by splashes of these agents on the nostrils and the back of the hand, respectively, i.e., the sites of the subsequent cancers. The development of the neoplasms, after the traumatic injury to the chronically exposed and altered skin, was, in both instances, very rapid, occurring within one week. Huguenin opined that the burn elicited the neoplastic reaction in a skin sensitized by preceding exposure to mazoute; as, in his case, the burn involved a freshly cicatrized area resulting from a former deep burn and containing a small papule before the accident. In both cases there seems to be sufficient reason to conclude, that the accidental burn merely accelerated the onset and development of an occupational tar cancer present in the skin in a dormant or submacroscopic stage.

In a third case noted by Gunsett, a burning piece of asphalt, injuring the external side of a thumb, caused the development of an ulcer which did not heal, but became transformed, in the course of three months, into a nodular mass of almond size. As Gunsett pointed out that the individual affected had an intact skin prior to the accident, the neoplastic reaction must be regarded as an unusually rapid developing pitch cancer. An inflammatory reaction, a retention of some of the carcinogenic material in the wound, and an individual hypersensitivity may have combined to bring about this unusual acceleration of a neoplastic reaction to asphalt. In all three cases cited the resulting tumors were spinous cell carcinomas.

XIV. HISTO-PATHOLOGY

Since more acute, cutaneous reactions to tar and pitch (folliculitis, perifolliculitis, comedones, pustulous dermatitis, and simple erythroderma) apparently have no causal relation to the subsequent formation of malignant lesions, and do not vary histologically from similar manifestations of different origin, a description of morphologic changes produced by these non-specific, irritative responses in the skin of tar and pitch workers may be omitted. Of direct significance and essential importance, on the other hand, are chronic atrophic and hyperplastic, epithelial lesions and chronic pigmentary disturbances, as gradual transitions lead from them to malignant manifestations; and, thus, endow them with the quality of precancerous responses, which possess more properties of a dermatosis than of a dermatitis.

a) Precancerous Lesions. It is characteristic of the action of tar and pitch to produce both atrophic and hyperplastic processes in the epidermis. In atrophic areas the skin appears grossly thinned and glistening, and covered by a thickened, cornified layer arranged in lamellae under which is found a wide zone of cells with prominent kerato-hyaline granules. In place of the

normal, spinous-cell layer, 2 to 3 rows of highly swollen cells with spines are present, while the basal layer is composed of one row of polygonal cells with large, vertically placed nuclei. These cells contain melanin pigment and rest, as a sharply demarcated layer, on a well-defined, connective tissue. The papillae are smoothed out due to an atrophy of the germinative cells, causing the epidermal base to form a straight line. Large pigmented chromatophores are found near the basal-cell layer in the derma. Occasionally lymphocytic and plasma cellular, perivascular infiltrations are observed. There are no changes in vascular walls, elastic fibrils, and sweat glands. The hyperkeratotic, cornified layer extends into the follicular ducts, sometimes plugging and distending them.

The hyperkeratotic and hyperplastic lesions exhibit a marked thickening of the cornified layer which forms a solid mass or a lamellated, cornified coating, the individual lamellae being separated from each other by empty spaces. The granular and spinous-cell layers are broadened and the granular cells contain numerous, kerato-hyaline granules. The germinative zone is composed of several layers of cells containing numerous, mitotic figures as evidence of an increased proliferative activity. The rete malphigii shows an intercellular edema. The papillary body becomes thick and edematous, and contains a dilated capillary network, while the individual papillae become longer. There occur discrete, perivascular, lymphoid and plasma-cellular accumulations in the derma. Some perivascular cells are of endothelial origin and may assume the character of giant cells. A disorderly arrangement of the cells is observed in the epidermis when proliferative manifestations are more advanced. The epithelial cells are then more atypical in type and are affected by parakeratotic changes. Epidermal pegs and cords of basal cells surrounding spinous-cell centers extend into the subepidermal tissue. A tendency toward concentric cellular arrangements and the formation of cornified pearls is noted in the central portions of these pegs. With the appearance of an increasing loss of cellular polarity and of a more active, infiltrative growth, these epithelial proliferations may assume ultimately morphological characteristics of a malignant, neoplastic growth. Sometimes, the cutis contains, at this stage, areas of mucoid degeneration of connective tissue, indicated by a bluish staining. Sweat glands, blood vessels, and elastic and collagenous fibrils are, in general, unchanged in the lesions described. The round, cellular infiltrations vary greatly in number, type, and distribution with different manifestations. They may be scanty or numerous, focal or multiple, and diffusely disseminated, or form solid, stripe-like areas in the subepidermal tissue. Often, the ducts of hair follicles are filled and distended by cornified matter which comes from the surface layer. The epithelium of follicular ducts may be vacuolated and atrophic or hyperplastic. The epithelium of hair follicles and sebaceous glands may exhibit atrophic changes when the plugging of follicular ducts has been prolonged. The epidermis, surrounding the ductal openings,

frequently exhibits a localized, increased proliferation shown by the formation of fine, digitiform processes of small, round, hyperchromatic, epithelial cells. These may surround foci of concentrically-arranged, spinous cells with central cornifications.

Accompanying these cellular changes, alterations occur in the pigmentation of the epidermis and subepidermal tissue. Brown, granular pigment, giving a positive dopa reaction for melanin, appears in all layers of the epidermis, a condition normally found only in the skin of Negroes, in whom the presence of pigment is not restricted to the basal layer. In addition to this fine, granular pigment found in and between epidermal cells, dopa-negative, brown, pigmentary deposits are noted in the cornified layer and in follicular cells. The pigmentation of the basal layer in hyperplastic areas is frequently less dense than in atrophic adjacent regions. The subepidermal connective tissue contains numerous, heavily-pigmented, chromatophoric cells which may form tumor-like conglomerations. The coarse, brown, pigmentary granules are dopa negative. The sharply delineated, elongated, or elliptical, chromatophoric cells, which possess, in general, no processes, are most markedly accumulated in the upper and middle part of the cutis, especially in the vicinity of vessels and follicles. The rete displays a moderate number of pigment-carrying cells.

The origin and character of this dopa negative pigment is still controversial. Bettazzi and others claim that it is derived from tar, and Kissmeyer even speculated whether tar contains substances chemically similar to cyclic amino acids, such as tyrosine which the body normally uses as a melanogen. Other investigators (Meirowsky; and others) contend that a direct formation of melanin, without the aid of an oxidizing ferment (poly-phenolase or dopa oxidase) capable of oxidizing bi-hydroxylated benzol derivatives, is possible, and causes the production and presence of dopa negative pigment in chromatophores of tar skin. These are the histological changes recorded by Bettazzi; Ullmann; Hoffmann; Schärer; Schamberg; Caligaris; Meirowsky; and Foerster and Schwartz in connection with their studies of precancerous lesions in the skin of tar and pitch workers.

The definitely malignant, cutaneous lesions observed in man, which are derived mainly from hyperkeratotic warts and rarely from papillomas, are, as a rule, cornified, squamous cell cancers displaying common, morphological features of such tumors. Basal cell carcinomas have been recorded in a few instances (Ullman; Bettazzi; and Barthe).

XV. EXPERIMENTAL TAR AND PITCH CANCER

The successful, experimental production of tar cancer is of great scientific, medico-legal, and historical significance, as it represents the first experimental causation of a malignant growth by a known chemical agent. This opened a new era of cancer research on synthetic, carcinogenic hydrocarbons. In addi-

tion to these general and fundamental aspects of experimental tar cancer, its accomplishment supplied, for the first time, definite experimental proof of the occupational origin of cancers observed among several groups of workers exposed to tar, pitch, and related substances. The great, continued interest, which the original investigations of Yamagiwa and Itchikawa have aroused, is reflected in the great number of experimental studies on tar cancer which have followed their work. These investigations have covered numerous aspects important in regard to tar cancer and occupational tumors in general. In view of this fact, and considering that no industrial neoplasm has been studied experimentally as thoroughly as tar cancer, especially in connection with the effect which other exogenous agents may exert upon its genesis and course, a comprehensive presentation of data on experimental tar cancer is essential and pertinent. The information supplied by experimental investigations is of distinct value for confirming, adjudging, and supplementing observations made in man, particularly when the evidence available is controversial or defective.

Historical Aspects. Many failures preceded the successful production of tar cancer by Yamagiwa and Itchikawa in 1915. Hanau (1889) and Lubarsch (1890) applied tar to rats for several months without obtaining any neoplastic responses. Negative results were recorded by Cazin in 1894 after painting dogs with tar for a corresponding period of time. Brosch applied this agent to the skin of guinea pigs for 3 to 4 months without eliciting any cutaneous tumors (1900). Stahr painted mice, rats, and rabbits with soot, tar, and xylol-paraffin without success (1907). Ullmann rubbed paraffin oil into the ears of rabbits (1912), and Haga (1913) applied pitch to the scrotum of these animals without obtaining tumors. These failures were due, in part, to the use of species of animals possessing a more or less marked resistance to carcinogenic action of agents employed, but mainly, to an insufficiently long period of application. Therefore, success came when Yamagiwa and Itchikawa repeatedly painted the ears of rabbits with hard coal tar for many months until metastasizing carcinomas appeared at the sites of application. These results were confirmed, subsequently, by numerous investigators using rabbits and other species of animals (Tsutsui (1918); Bloch; Bierich; Itchikawa; Deelman; and Teutschlaender; in mice). The first experimental production of pitch cancer in mice was accomplished by Kennaway who obtained 9 tumors (3 papillomata, 6 epitheliomata) among 27 survivors of 100 mice treated with a suspension of pitch in lanolin. These results were substantiated by Leitch who used a suspension of pitch in sebum, and were elaborated upon by Kennaway and Jordan who, by applying a solution of pitch in benzol to the skin of mice, produced cutaneous malignancies.

Constitutional Factors (Differences in the Susceptibility of Various Strains and Species). In numerous attempts made to confirm and extend the original observations of Yamagiwa and Itchikawa, and Tsutsui, marked variations in

the susceptibility of animals belonging to the same species (rabbits and mice) were noted. Renand did not obtain a single tumor among 130 mice treated for 17 months with cutaneous applications of tar. Dentici observed only 2 tumors among 86 mice tarred for 239 days. It is obvious that these results do not reflect an intrinsic refractoriness of the mice used, but are attributable to the employment of a tar lacking in carcinogenic potency. However, the investigations of Lynch, 1928; Korteweg, 1933; Parodi; Kreyberg; and Reinhard and Candee indicate that hereditary, genetic factors may account for differences in susceptibility of various strains of mice to the carcinogenic action of tar. Woglom estimated that about 70 per cent of the mice surviving for more than 4 months develop cancer regardless of the length and intensity of their exposure to tar. Borst was sceptical about the possibility of producing experimental tar cancer in 100 per cent of the animals treated with this agent. This investigator contended that reports of such results were probably due to incorrect, histological diagnosis. Observations recorded by numerous other investigators indicate that cancers can be produced in 100 per cent of mice treated adequately with a potent tar and surviving sufficiently long (Fibiger; Bang; Beck; Joannovič; Deelman; Teutschlaender; and Maisin). These conclusions are in accord with those of Branch; Boyland and Warren; Dobrovolskaia-Zavadskaia and Garrido; and Andervont, who investigated this question in mice using several, synthetic carcinogens (dibenzanthracene, methylcholanthrene) for this purpose. Although there were differences in the reactivity of diverse strains to these agents, manifested, sometimes, in variations of the length of the preparatory period necessary for the induction of the neoplastic response, Andervont claimed that these genetic differences disappear, when sufficiently high doses are used because animals of different strains become uniformly susceptible under such conditions. The use of tar with a low potency may account for differences observed in the susceptibility of different strains of mice possessing different reactivity thresholds for tar.

Among the various hereditary and constitutional factors, which have been investigated to determine the origin of such differences in susceptibility among several strains of the same species, the color of the hairy coat has attracted some attention. This is due to the pigmentary disturbances observed in man in connection with exposure to tar and pitch, and to the higher resistance of dark-pigmented races to tar and pitch cancer. It has been claimed by Yamaguchi, Nishiyama and Suzuki; Marchlewski; Grynfeltt and Harant; Ściesiński; Suzuki; Fukuda; and Reinhard and Candee that mice and rabbits having a deficiency or lack of pigment (white or albino animals) are more susceptible to tar than those showing a definite degree of pigmentation (grey, brown, or black). These contentions have been contradicted by Yamagiwa and Itchikawa; and Leroux, who found the opposite relation existing between coat color and reactivity to tar. More recent studies by Dobrovolskaia-Zavadskaia and Olch on 118 mice, belonging to 13 different, but genetically-known strains of mice

possessing various colored hair coats (white, grey, brown, and black), indicated that no constant relation exists between degree of pigmentation and reactivity of a particular strain to the carcinogenic action of tar. In a subsequent investigation dealing with the same question, these investigators were able to produce precancerous as well as cancerous lesions with tar in all 16 strains of mice studied, differing in their tendency toward spontaneous carcinogenesis and in the color of their coat. They concluded that a pigmented skin does not afford a safe protection against the carcinogenic action of tar.

The relatively frequent existence of an hereditary tendency of mice to spontaneous tumor formation in various internal organs (mammary gland, lung, and liver) has offered an opportunity to investigate the possible effect of such a property upon susceptibility to carcinogenic action of tar upon the skin. Reinhard and Candee as well as Kreyberg stated that any constant relationship does not seem to exist between carcinogenic action of tar on the skin and the presence of a genetic susceptibility to a spontaneous cancer development. Reinhard and Candee found a delayed neoplastic response to tar in a strain of mice with a low tendency toward spontaneous carcinogenesis. However, Kreyberg reported the presence of an opposite interrelation, as tar cancers seemed to appear precociously and more frequently in a strain of mice exempt from spontaneous tumors. Dobrovolskaia-Zavadskaia and Olch recorded a similar observation in a brown strain of mice refractory to spontaneous, mammary neoplasia. Parodi; Truffi; and Lynch noted, on the other hand, that the presence of a tendency toward spontaneous, mammary cancers does not interfere with the formation of tar cancers of the skin. Also, the production of these neoplasms does not prevent or influence the development of spontaneous, mammary carcinomas in mice, contradicting a statement made by Murray. The observations made by Parodi; Truffi; and Lynch, concerning the interrelations between tar cancer of the skin and spontaneous, mammary cancer, were substantiated by Bonser and Connal. These two stated that the presence of a tar cancer did not delay the appearance of spontaneous, mammary tumors in mice nor did it diminish their incidence. A similar lack of correlations was found to exist between relative susceptibility to spontaneous, mammary malignancy, and induction of subcutaneous sarcoma by dibenzanthracene and methylcholanthrene in mice (Andervont).

It has been established that application of tar to the skin of mice may increase, by direct or indirect action, the incidence, and hasten the appearance of the so-called spontaneous, pulmonary adenomas and carcinomas.

Murray advanced the claim, at one time, that the skin of mice which surrounded a tar cancer was refractory to the carcinogenic action of tar. This contention could not be substantiated in subsequent experiments by Murray himself or by Parodi; Truffi; and Lynch, who noted that the presence of a tar cancer at one site did not convey an immunity to the production of additional cancers upon some other parts of the skin. It was shown, however, by Bang that

mice with lowered vitality, and suffering from severe, general poisoning by tar were less apt to develop skin tumors than animals vitally unimpaired.

A great deal of effort and speculation has been expended in attempts to shed some light upon the causative mechanism which is responsible for the remarkable differences noted in the susceptibility of various species to carcinogenic action of tar. Production of tar cancers was accomplished rather readily in mice and rabbits; however, great difficulties were encountered when attempts were made to obtain similar results in the closely related species of rats. An appreciable number of investigators (Buschke and Langer; Borrel; Itchikawa; Boez and de Coulon; Itchikawa and Baum; Yamagiwa; Calvanico; Halberstaedter; Deelman; Teutschlaender; Möller; Joannovič; Bonne; and Neumann) failed to elicit any neoplastic reactions in rats subjected to prolonged, cutaneous applications of tar. Consequently, for some time the opinion prevailed that rats were entirely refractory to tar.

In recent years, several investigators succeeded in obtaining cancerous responses in the skin of rats after very extended applications of tar. Dentici (1923) found one papilloma in one out of 30 rats, after 176 days of cutaneous treatment with tar. Herlez (1926) reported one carcinoma among 100 rats, painted for 511 days with a mixture of coal tar, glycerol, and arsenious acid. Cholewa (1929) succeeded in developing one cancroid in 10 rats subjected for seven months to repeated scarifications of the skin by burns, on which tar was applied the following 5 months. Guilera, Roca, and Corachán (1930) found one cancer among 40 rats painted with tar. Watson reported that of 11 rats treated cutaneously with ether extracts of rat tissue, followed by paintings with gas-house tar, four developed squamous cell carcinomas with extensive metastases. Papillomata appeared in these animals after 415 days of treatment; malignant tumors were present after 630 days. Giuffrida (1930) also, obtained positive results in rats after paintings with tar. It appears that the difference in reactivity to carcinogenic tar existing between mice and rabbits, on one side, and rats, on the other side, is not of a fundamental nature, but merely a matter of degree.

Attempts to produce tar cancer in the skin of guinea pigs have failed, according to reports of Leitch; and Neumann. Similar, negative results were obtained in regard to dogs by Itchikawa; Itchikawa and Baum; Dentici; Borrel; Boez and de Coulon; Bloch; Teutschlaender; and Halberstaedter. Recently, however, Passey recorded the successful production of malignant melanomas of the skin in three dogs which had received tar applications for more than 6 years. This result is the more remarkable, as the development of melanotic tumors by cutaneous treatment with tar appears to be highly exceptional and somewhat controversial in regard to the actual, neoplastic nature of the melanotic accumulations obtained. Only Lipschütz made a similar claim in connection with neoplastic responses seen after tarring the skin of grey mice.

Attempts of Bonne, Lodder, and Streef to elicit cancerous responses in the skin of monkeys from Java (Macacus cynomolgus) by the application of gas house tar to the backs of these animals for periods of one to one and a half years, led to the formation of broad-based papillomata and a general thickening of the epidermis. While the histological examination of these excrescences suggested a malignant character, they promptly improved after the cessation of the treatment with tar, even exhibiting this tendency during the time these applications were carried out.

The underlying factors of the species specific differences are still obscure. Some investigators suggest that these discrepancies may be caused by fundamental differences of the various species in the structural character of the skin; i.e., vascularity of the subepidermal, connective tissue. While quantitative as well as qualitative differences of this kind actually exist, there is no sound, reliable evidence available, indicating that such distinctions in the character of subepithelial, connective tissue are the cause for different reactivity of overlying, epithelial cells to the carcinogenic action of tar. Although it is conceivable that a meager vascularity of subepidermal tissue does not favor a proliferative response of the epidermal cells, it seems improbable that such a condition would be, normally, so marked in some species that it would completely prevent a cancerous response to tar.

Some investigators correlate the variations of the susceptibility of different species to tar to their respective, normal-life span. They contend that the length of the preparatory period, necessary for the induction of a malignant response to tar, depends directly upon the life span of the species involved (Woglom). Bang stated that the average, preparatory period of a tar cancer in a mouse is from 8 to 9 months, or, approximately, one-third of the normal-life span of this animal, corresponding with the 20 to 30 years of latency period of tar cancer observed in man. Passey noted that susceptibility of dogs to tar cancer was about the same as that of men and mice, as six years were required to elicit a malignant response in the skin of a dog, having a normal-life expectancy of 16 to 23 years.

The relative merits of this conception are illustrated well by the following data: The *shortest* latency period of tar cancer for the mouse is 50 days; for the rabbit, 47 days; for the rat, about 400 days; while the guinea pig is entirely refractory. The *maximum* latency period for the mouse is 540 days; for the rabbit, 560 days; for the rat, more than 500 days. The *average* latency period for these species is recorded as 120 days for the mouse, and 150 days for the rabbit. The latency periods for tar papillomas do not follow the same pattern. The minimum period for mice is 60 days; and for rabbits, 30 days; while the maximum period for mice is 393 days; and for rabbits, 100 days (Woglom).

Twort and Twort estimated the intrinsic susceptibility of various species to the action of carcinogenic, tarry agents by gauging the rapidity and the amount

of epithelial hyperplasia observed in response to the application of these agents to the skin. These investigators constructed from their data the following scale of susceptibility: when the susceptibility of the rabbit was taken as 1, that of the mouse was 100, that of the rat 3,000 and that of the guinea pig 1,000,000. The investigators conceded that, possibly, the hyperplastic response might not run parallel to the carcinogenic one. The concept that normal-life span, length of preparatory period, and, in part, susceptibility of various species to the carcinogenic action of tar are directly correlated receives little, if any, support from actual, experimental facts. It simply appears to be one of the several, devious methods of connecting the process of carcinogenesis with the physiological, aging process of the body, applied, in this instance, only to regressive changes associated with the normal life cycle of individual cells in various species.

Sex. Numerous observations, made in connection with the many studies of experimental tar cancer, indicate that sex is one of the intrinsic factors which does not play a role in production or susceptibility to these tumors.

Age. Age or, more appropriately, tissue senescence is another of the endogenous factors which has been found to be without influence upon the induction and development of experimental tar cancer, according to Fibiger; Roussy; Döderlein; Leroux and Peyre; Bang; Leitch; Parodi; and Woglom. Young animals of both sexes reacted, upon the application of tar, as readily with the development of cancer as adult individuals, demonstrating that a physiological, local or general, tissue senility is neither an essential nor a secondary contributory factor in the development of these neoplasms. Bang pointed out that the long latency period usually required for the production of experimental and occupational tar cancers was evidently responsible for the advanced age of the affected individuals.

Extrinsic Factors. In addition to endogenous factors mentioned, a great number of exogenous factors were investigated to determine their possible effect upon the causation and course of tar tumors in animals. The factors and agents tested were the following: type of tar, temperature of tar, concentration of tar, size of tarred area, duration of tarring, interval between applications of tar, and simultaneous or preceding exposure to various, exogenous, carcinogenic and noncarcinogenic agents (solar rays, ultraviolet rays, roentgen-rays, radioactive substances, scarring and burning of skin, arsenic, xylol, benzol, lard, and lanolin). The study of complicating conditions of the types listed is not only of scientific importance, but of immediate, practical significance, as such factors are operative, partly, as some of the normal or accidental, environmental influences during the development of industrial tar cancer, and partly, are applied to the skin with tar dermatosis during the therapeutic management of tar neoplasms in man. Since a well-controlled investigation of the rôle these agents played in the causation of these tumors could not be conducted

in man, the needed information had to be obtained through the experimental approach with the use of animals.

Type of Tar. High-temperature tars, such as those produced in horizontal retorts of gas works, have been found through experiments with animals to be, in general, more carcinogenic than low-temperature tars. As Kennaway proved that a low-temperature tar, prepared from acetylene, exhibited a higher, carcinogenic potency than several high-temperature tars, obtained from coal, isoprene and skin, a constant relation between these two factors does not exist. Coal tar presumably possesses a higher carcinogenic power than vegetable tar. Nevertheless, Watson prepared a pinene tar by pyrolysis of terpentine oil, which proved to be of higher potency to mice than a gas-house tar. Twort and Fulton could show that the carcinogenic potency of pinene tar depends upon the temperature of distillation. Flory obtained papillomas and carcinomas in mice and rabbits painted with destructive distillates of tobacco and pipe tar. These investigators observed that pinene heated in a nitrogen atmosphere showed a gradual increase in carcinogenicity between 500°C to 850°C, but exhibited, upon further heating (up to 950°C), a loss of its carcinogenic potency amounting to one-third of its peak value when tested on mice. Not only the temperature of pyrolysis, but also, the character of the material used in the production of tar greatly influences the carcinogenic potency of this substance. Thus, the experimental results obtained by different investigators employing various types of tars are not strictly comparable. Similar considerations must be applied to the occurrence and incidence of industrial tar and pitch cancer.

The carcinogenic potency of a particular type of tar is not the only factor which determines the intensity of exposure; the concentration of tar, the frequency and number of applications, the temperature of the tar when applied, and the size and site of the area painted are, also, of great importance.

Concentration of Tar. Seelig and Cooper noted that excessive dilution of cancerigenic tar with glycerin causes diminution and, finally, loss of carcinogenic activity. Hieger made similar observations when he obtained a decrease in tar cancers, while applying to the skin of mice a carcinogenic tar in various dilutions. This investigator painted one series of 50 mice with a pure (full strength) ether extract of carcinogenic tar; a second series, with a 10 per cent dilution; and, a third series, with a 1 per cent dilution. The induction time for cancer development was much longer for series III than for series I and II, and the total number of tumors produced in III was much smaller than in I and II. The animals of series II, however, exhibited a very slight delay in the appearance of neoplasms when compared with series I.

A similar experiment was conducted by Woglom, who applied to the skin of mice a horizontal gas-house tar distilled at 1,000°C. The tar was used full-strength, and in concentrations of 75 per cent, 50 per cent, and 25 per cent

by diluting it with glycerin. The tarring was discontinued, when an infiltrative growth of the lesions produced was noticed. While 53 per cent of the mice treated with concentrated tar developed neoplasms, the yield of the three series exposed to various dilutions was practically identical (32 per cent, 33 per cent, and 40 per cent, respectively). There was no reduction in preparation time in the three series subjected to diluted tar. These experiments did not confirm completely the observations of Hieger; but Woglom noted that results of unfinished experiments indicated that the critical point of dilution seemed to lie between a 1 per cent and a 10 per cent dilution. Twort and Ing stated that the use of graduated, increasing dilutions of tars or mineral oils, which only contain a relatively small amount of carcinogenic matter, resulted in a more rapid reduction of their carcinogenic potency, than could be expected from the degree of dilution used. It was emphasized by Hieger, on the other hand, that, after the concentration of the carcinogenic agent had passed a certain degree, the neoplastic yield could not be increased and the induction time could not be shortened beyond a certain limit.

These observations stress the importance of prompt removal of tar and pitch from the skin of exposed workers to reduce intensity of exposure, decrease liability to neoplastic reactions, and lengthen exposure time essential for their production. These experimental data agree with clinical observations, inasmuch as occupational tar and pitch cancers are found, most frequently, in those groups of workers who are the most intensely exposed to these agents. They seem to confirm the statement of Kinosita regarding the influence of cleanliness of Japanese tar workers upon the occurrence of occupational tar cancer in Japan.

Interval Between Tarrings. The influence which the length of the interval between individual applications of tar exerts upon the time of onset for the manifestation period was studied by Deelman. This investigator painted with tar from 17 to 22 times six groups of mice, leaving from 1 to 8 days interval between the applications in the different groups. While the time of exposure ranged in the various series from 44 to 140 days, from the start of the experiment, cancers appeared in all groups within 50 to 60 days. The development of the malignant tumor, thus, appeared to be a function of a summation of stimuli. Woglom concluded from this evidence that malignant transformation sets in and proceeds inexorably after the cumulative effect has reached a certain level, whether the irritation is continued or not.

Duration of Tarring. The duration of application of carcinogenic tar to the skin of animals is of essential importance, concerning the incidence and biological character of the ensuing neoplastic responses. Yamagiwa and Itchikawa obtained papillomas in rabbits after painting them every second or third day for 30 to 100 days, and carcinomas resulted when the tarring was continued for 55 to 360 days (150 or more days were required in the majority of cases). By observing special precautions and using massive doses, Itchikawa and Baum

produced tar cancers in rabbits as early as 47 days after the start of the experiment, precancerous lesions being present in 92 per cent of the 24 rabbits at the 80th day of treatment, the earliest lesion of this type being noted on the 35th day. Ciechanowski, Morozowa, and Wilhelmi attained precancerous responses in rabbits within 30 days, and Babès claimed to have produced tar cancer in rabbits after the exceedingly short time of 13 to 19 days of tarring. Peyre and Kotzareff, also, observed the formation of malignant lesions in rabbits after a short period of tarring (36 days). Seelig and Cooper stated that 25 days was the shortest latency period of experimental tar cancer recorded. Beck reported that papillomas appeared in rabbits after tarring for 7 to 11 weeks, while carcinomas developed after 4 to 7 months of this treatment, the incidence increasing with the time of exposure (92 per cent of the survivors having malignancies after 4 months, and 96 per cent, after 6 months of painting).

Similar observations about variations in the length of the latency period of neoplastic reactions, and their partial dependence upon the duration of treatment were made in regard to mice. Tsutsui, who was the first one to produce tar cancer in mice, stated that these neoplasms appeared after tarring for 100 days or more. Fibiger noted that papillomas developed after 86 days of tarring and cancers after 257 days in 100 per cent of the surviving animals. Lipschütz as well as Truffi found that 90 to 150 days of tarring were required for the production of papillomas, while Fibiger and Bang noted that a period of 4 to 8 months of this treatment was needed for eliciting these responses, whereas cancers appeared after tarring for, at least, 5 months. Similar time relations were recorded by Bierich and Möller, while Deelman as well as Foerster obtained cancers after 50 to 60 days of tarring. However, the latency period was prolonged from 8 to 10 months when tarring was discontinued after 2 to 3 months, instead of being kept up for, at least, 4 months. Bang demonstrated the effect of the duration of tarring upon the incidence of resulting cancers in the following experiment:

Duration of Tarring	Number of Mice	Number of Carcinomas
1 Month	14	0
2	16	3
3	13	9
4	12	12

Mice painted for one month only may escape cancer entirely, while those painted for 4 months develop it 100 per cent. The intermediate group, with exposures of 2 to 3 months exhibits neoplastic responses in only those animals which are especially susceptible. The freedom of the animals with apparently insufficient exposure from cancerous reactions is not proof that this agent has not exerted some preparatory effect upon the skin, which may manifest itself

by the delayed appearance of a tumor long after the cessation of treatment (Deelman). This investigator has demonstrated this latent effect in experiments with rabbits in which he produced tar papillomas. Although these papillomas disappeared after the tarring was stopped, new neoplasms appeared more readily in these animals, when the treatment was resumed several months later, than in rabbits receiving tar applications for the first time. These experimental observations confirm similar, circumstantial, clinical evidence repeatedly noted in tar and pitch workers, and are in agreement with results obtained by the cutaneous application of synthetic, carcinogenic hydrocarbons (Mider).

Type of Contact. Experimental tar cancer of the skin has been produced by applying tar dissolved in some organic solvent (benzol and ether) or fatty matter (lard and lanolin), and upon the exposure of mice to tar in the form of dust (Bonne; and Campbell). Campbell, who obtained warts in dusted animals after 186 to 248 days of treatment, noted the following facts: the length of the latency period apparently depended upon the concentration of the tar in the dust; the number of papillomas increased with the duration of exposure; and these neoplasms were at sites where tarry dust settled the most (head and back; rarely neck, abdomen, and limbs). Carcinogenesis from exposure to tar dust is influenced, in these respects, by the same factors operative in the formation of tar tumors after contact with liquid tar.

The influence of parenterally introduced tar upon the development of neoplasms in the skin subsequently painted with tar was studied by Maisin and Marse; Martin; and Daels. Maisin and Marse observed that the development and incidence of papillomas and carcinomas were greatly enhanced when tarring of the skin of the neck of mice was preceded by subcutaneous injection of tar into the skin of the abdominal region. Similar results were obtained by Martin, when an intravenous injection of tar was followed by repeated, intracutaneous injections of this substance. These investigators asserted that they had proved that tar, parenterally introduced at points remote from the site of a subsequent, cutaneous contact, exerts a systemic and sensitizing effect.

Such activating effects were not observed when the parenteral introduction of tar was made at that part of the skin which was tarred subsequently (Daels). Daels implanted small pieces of tarred skin into subcutaneous tissue, and passed tarred threads through the skin which was later subjected to the application of tar. Since neoplastic responses were better in non-treated, control mice than in those subjected to a previous, traumatic injury by tar, Daels concluded that the production of cicatricial changes in subjacent, connective tissue of tarred skin reduced the disposition of the epidermis to undergo malignant changes.

These observations on the local and general effect of parenterally introduced tar are of great practical importance. They are closely related to the rôle which a nonspecific, physical trauma to the skin is alleged to play in the produc-

tion of tar tumors, when acting upon a skin previously exposed or subsequently subjected to tarring.

Trauma. Experiments dealing with the interrelation between a thermic injury and tar neoplasia are of special significance, as the combination of cutaneous contact with tar and accidental burns is often met with in tar workers, and has given rise to the claim that tar cancers develop rapidly, following burns in a tar-exposed skin (acute, traumatic tar cancer).

Derom reported that the application of a tar of 70°C to the skin of animals yielded more tar tumors than a tar of 37°C would. Rémond, Sendrail, and Boulicaud emphasized the prompt development of cancerous responses in rabbits painted with a tar heated to 50°C. Raposo observed that a tar which did not elicit any tumors in 45 rabbits when cold, caused the development of cancer in 9 out of 35 rabbits treated when this tar was 55°C (cold tar series: 70.5 per cent hyperplasia, 29.5 per cent papillomas; hot tar series: 47.5 per cent hyperplasia, 37.5 per cent papillomas, 15 per cent cancer). Contrary to this, Choldin recorded that the application of tar heated to 50°C and 80°C to the skin of albino mice caused the development of large necroses, and an initial, but transitory delay of the appearance of tar cancers. This was followed by an unusually rapid, subsequent growth of these tumors.

Similar observations were made when thermic or some other kind of physical or chemical trauma was caused in a previously tarred area, or was followed by tarring before a firm scar had developed. Rous and MacKenzie found that punching holes into the ears of rabbits previously treated with tar, until papillomas developed, which were permitted to recede after cessation of the tarring, resulted in the appearance of new tumors within the area of the healing defects, especially in their marginal portions. A similar effect was elicited when turpentine oil was applied to the tarred skin of rabbits, rendered potentially neoplastic in the described manner. These observations of Rous and MacKenzie substantiated similar ones made previously by Deelman, who scarified the skin of mice, which had been painted with tar, until small, localized hyperplasias had developed. The papillomas developing in the scarified tissue of the majority of mice grew rapidly and were, in many instances, very malignant. Cramer found that injury to the connective tissue of the tarred skin of mice was followed by a transformation of the hyperplastic epithelium of papillomas into a malignant one. Carcinomas developed within 42 to 53 days in the ears of rabbits whose inner surfaces were tarred, after developing a good, epithelial growth following repeated scarification (Raposo).

MacKenzie and Rous concluded, from the evidence of their own experiments and those of others, that cells of tarred skin may become neoplastic in considerable number, yet never manifest themselves unless aided by extraneous influences, such as a trauma may provide. These observations are considered important from a medico-legal standpoint concerning the rôle trauma may play in cancer production.

Cancer formation was observed in the traumatized skin of mice, when burns or scarifications were made at places remote from the tarred areas (Kreyberg; Polettini; and Akimoto). While these experiments usually demonstrated a systemic effect of local tar applications, they represent additional evidence for the activation of neoplastic growth by direct application of tar to freshly injured tissue. In the evaluation of such experimental results proper consideration must be given to the fact that in small animals, such as mice, the tarred area is in relatively close proximity to the scarified or burned area. This permits the rather ready direct or indirect transfer of tar applied to the injured skin by licking, rubbing, and scratching of the tarred area, especially if several mice are kept in the same cage, which will, thus, be filled with a fair amount of tar containing dust.

Experiments of Ludford; Bang; Bonne; Derom; Raposo; Giuffrida; and Koose and Cordes showed that cicatrized skin is more resistant to the carcinogenic action of tar than normal skin. It is noteworthy that Bang did not succeed in producing cancers in mice whose skin had been tarred once and burned afterwards, or had been treated with boiling tar once. Several investigators, using rabbits in their tests, failed to obtain support for the conception of a sensitizing, systemic effect of tarring upon the neoplastic development in scarified or burned areas of the skin, located remotely from the area painted with tar. Bonciu and Guérin, who tarred the inner surface of one ear of 14 rabbits, and produced burns by applying a red-hot, glass rod to the other ear, obtained cancers in the tarred ears, and, merely, epithelial hyperplasias in the burned ears. Under these experimental conditions, the mechanical transfer of tar from one ear to the other is difficult, and, for this reason, these observations provide more valid evidence than those obtained in mice.

Application of tar to an epidermis covering a fresh scar tissue, i.e., a delicate loose, well-vascularized tissue, or production of a moderate, inflammatory response by physical or chemical means in a tarred skin, may hasten the development of tar tumors, may increase their incidence, and may induce the transformation of previously benign tar papillomas into malignant growths, by activating dormant potentialities. It is possible that such local injuries, enhancing the vascularization and, thereby, the blood supply of restricted areas, may predetermine the site of future, neoplastic growths within a larger tarred area (Deelman). Severe traumatization, resulting in extensive tissue destruction and old, sclerotic, poorly vascularized scarring, appears to create environmental conditions impairing nutritive conditions of tissue essential for neoplastic response to tar. It is probable that local variations in the vascularization of different parts of a tarred area are responsible for the appearance of neoplastic proliferations on isolated points, and not throughout the entire area.

Site. Similar considerations have been advanced to explain apparent discrepancies in the susceptibility of different parts of the skin to tar cancer. Cie-

chanowski and Ściesiński claimed that tar cancers developed more quickly and more numerously in the ears of rabbits than in the skin of the back because of a lower vascularization of the skin of the back, where tar cancers never grow infiltratively nor metastasize, according to these investigators. Even though Teutschlaender produced scrotal cancer in rabbits by the application of tar to this part of the skin, additional evidence shows that differences in the susceptibility of various parts of the skin in rabbits is not of fundamental nature, but more a matter of degree.

The skin of the interscapular region of mice presumably represents the most sensitive area of the skin, as to tar cancer development. This local preference of tar cancers is a spurious one. Mice cannot remove the applied tar from the interscapular region by licking or scratching and, for this reason, tar can act more intensively and longer here than in other parts (Burckhardt). Roussy was unable to show any difference in susceptibility between various regions of the skin in mice to the carcinogenic action of tar.

Size of Tarred Area. Woglom cited statements of Itchikawa and Bervin; and Deelman to the effect that tarring of large areas hastens the development of tumors; while Murray was unable to observe such an influence. Through reinvestigation of this aspect by Schär, who painted, in several series of mice, areas of different size with tar, the conclusion was reached that the time of the appearance of papillomas was the same in all series, regardless of the size of the tarred area; but the number of these tumors formed increased in proportion with this factor. Carcinomas, on the other hand, appeared only in animals with large, tarred areas and showed an incidence paralleling the size of the area painted.

Effects of Solar Radiation and Ultraviolet Rays Upon the Development of Tar Cancer. The marked photosensitivity displayed by individuals with occupational contact with tar and pitch has raised the question, as to whether solar rays are an essential or important, contributory factor in the causation of tar and pitch cancers (Büngeler), especially since these tumors most frequently involve exposed parts of the skin. The occurrence of occupational tar cancers in areas not exposed to sun-light made the obligatory rôle of this factor a doubtful one. Nevertheless, experiments have shown convincingly that these biologically active rays are not necessary for the development of tar cancers, as these neoplasms appeared readily in mice kept in total darkness throughout the entire experimental period (Teutschlaender; Seelig and Cooper; Schorr and Ssobolewa; Vlès and de Coulon; Fibiger; and Bang).

While the fundamental aspect of this question seems to be definitely decided, no unequivocal information is available concerning the action solar rays or ultraviolet rays may exert upon the developmental mechanism of these tumors. Neumann and Kohn-Speyer could not observe any influence of these rays upon the production of tar cancer. Seelig and Cooper; Doniach and Mot-

tram; and Teutschlaender, on the other hand, reported that mice kept in the dark had a higher incidence of tar cancers than mice exposed to sunlight. Other investigators (Büngeler; Findlay; Vlès and de Coulon; Dormanns; and Schorr and Ssobolewa) asserted that exposure to solar or ultraviolet rays hastens the appearance of tar cancer. It appears, from the evidence available, that this claim reflects conditions actually existing in this respect. It is conceivable that the hastening effect of solar and ultraviolet rays represents either the result of an additive carcinogenic action of these rays or is nonspecific and caused by the hyperemia and capillary hyperplasia, accompanying an actinic erythroderma. This is accentuated by chemical photosensitization through tar, and creates nutritive conditions in the skin favorable for cellular proliferation. Excessive actinic reactions, on the other hand, may set up environmental conditions in the tissues, such as necrosis and exudation, which impede the carcinogenic action of tar and delay the appearance of tar cancers.

Roentgen-Rays and Radioactive Substances. Similar relations apparently exist in regard to the action of roentgen-rays and rays from radioactive substances upon the development of tar tumors in animals. It is well known from clinical experience that roentgen-rays and radioactive rays inhibit the development of tar cancer in a skin containing precancerous tar and pitch lesions, and, also, destroy malignancies of this origin (London Letter; and Watson).

Certain experimental observations made during recent years suggest, however, that a general irradiation of tarred mice with small doses of roentgen-rays (160 to 1,440 r) may increase the yield and malignancy of the resulting tar cancers, and may hasten their appearance (Reinhard and Thibaudeau; London letter; Castiglioni; Domagk; and Cirio and Balestra). Similar observations were made by Mayneord and Parsons in regard to the formation of subcutaneous sarcomas, when mice injected with 1:2:5:6-dibenzanthracene-9:10-alpha-beta succinate were exposed to 550 r.

Maisin, and Ledecq and Estas noted that intravenous injection of ionium into tarred mice and rabbits caused an accelerated induction of tar cancers, and increased the incidence of metastases (60 to 70 per cent instead of 30 to 35 per cent in the controls, which were only tarred). Maisin claimed, moreover, that introduction of ionium prevented the spontaneous regression of tar cancers in rabbits which is, often, observed following the cessation of tar applications, i.e., the procedure brought about a change from a "histological malignancy" to a "physiological malignancy." It is believed that exposures to radiating energy of this type, given in suitable doses, break down the natural resistance of the organism against a neoplastic growth.

Contrasting results were reported by Stolz and Vanysek, who noted that the development of hyperkeratoses and papillomas in the tarred ears of rabbits was delayed, and quantitatively reduced, after the intravenous injection of radium emanation. Similar inhibitory responses were recorded by Maisin and Picard, when uranium and thorium were introduced into tarred animals. The

inhibiting action of radioactive substances exerted upon neoplastic responses were attributed, by these men, to a stimulation of reticulo-endothelial cells in which these chemicals are stored. Roussy, Leroux, and Peyre found that a preceding exposure of animals to filtered or unfiltered radium rays did not hasten the development of tumors caused by subsequent tarrings. These findings mainly possess a therapeutic significance, as radiating energy from roentgen-tubes and radioactive substances is used in combating neoplastic manifestations in the skin of tar and pitch workers. The experimental, recorded results suggest that the therapeutic application of inadequate doses of these agents to a skin with precancerous tar and pitch lesions may cause an activation of these manifestations, resulting in their malignant transformation.

Arsenic. Itchikawa and Baum contended that a medication of arsenic hastened the appearance of tar papillomas in rabbits, while it hindered the development of tar tumors in mice. To the contrary, Choldin reported that tar tumors occurred much earlier in mice which had been treated with arsenic before they were painted with tar, than in control animals which were tarred only. Since Teutschlaender; Fibiger; Fibiger and Bang; de Coulon; and Daels demonstrated, in refutation of the arsenic hypothesis of Bayet, that tars free from arsenic were carcinogenic and that the relative arsenic content of different types of tars was unrelated to the carcinogenic potency exhibited by these agents, it seems improbable that arsenic exerts any appreciable and significant influence upon the induction and development of tar cancers, unless special conditions are present.

Nature of Solvent and Preparation of Skin. Watson pointed out that the medium in which tar is dissolved may determine and influence, to a considerable extent, the carcinogenic action exerted by this substance. It is a general experience that agents such as lard, lanolin, various vegetable oils, paraffin oils, and similar solvents of tar reduce the carcinogenic effect of tar; while solvents such as benzol, xylol, ether, and chloroform, which dissolve the natural skin fat, apparently favor the penetration of tar into the skin, and accelerate its carcinogenic effect (Twort and Twort; Bittman; and Bartozek). The removal of the skin fat with ether, xylol, and similar substances, before tarring was undertaken, hastened the development of tar tumors in mice and rabbits (Jaffé and Eliassow); while the application of sodium oleate, lanolin, and paraffin delayed the appearance of these manifestations (Lecloux). These experimental observations supply evidence, which explains, plausibly, the higher resistance against tar and pitch of the oily skin of colored races in comparison to white races, and provides valuable information which may be used for devising effective methods for the protection of the skin of exposed workers.

Pathology of Experimental Tumors. The macroscopical and microscopical changes, observed during the course of tarring in the skin of mice, rabbits, and other animals, have been studied systematically and in great detail by many

(Yamagiwa; Kreyberg; Deelman; Guldberg; Maisin; Teutschlaender; Döderlein; Mottram; Leitch; Bloch and Dreifuss; Bierich; Roussy and Leroux; and Rous). The information concerning the character and sequence of various pathological alterations associated with the formation of experimental tar cancers is, for these reasons, more complete and extensive than that regarding the pathological aspects of occupational tar and pitch epitheliomas in man. A detailed presentation of the experimental data is pertinent, as these findings not only confirm and supplement the evidence obtained from industrial tumors of this type; but they, also, record, with greater coherence, the processes and factors contributing to the causation and development of tar cancers.

Macroscopical Changes. During the first month of tarring the skin reacts with an acute dermatitis, characterized by erythroderma, swelling, alopecia, epithelial desquamation, and the formation of superficial sores, which are rapidly reepithelized from the edges without hyperplastic, epithelial thickening. As these acute manifestations gradually subside, they are replaced during the second month of tarring by those of a chronic character. The originally white skin becomes grey, firm and thick (pachydermia), and attached to its base. Sometimes, the surface is smooth; at other times, it is furrowed.

After the second or hyperplastic stage, the third or neoplastic stage follows, which is characterized, in the beginning, by the appearance of small, circumscribed, slightly convex nodules possessing a shiny surface, and developing, later, into papillomata and warts. Some of these papulous nodules, which are usually multiple, remain small or they may even regress; while others grow into pedunculated or sessile papillomas. Frequently the tips of the papillomas develop cracks and excoriations. After several weeks of progressive growth, the warts and papillomas assume a stationary condition which is often followed by a period of regression. Some of the papillomas shrink and fall off, leaving small sores which heal in most cases; thus, only small spots of thickened skin remain.

With continued tarring new papillomatous growths appear, which may undergo the same cyclic changes as the first set, or may show, in part, a progressive development, such as seen in the first series of papillomatous formations. Döderlein stated that these papillomatous and warty growths may appear in several waves and showers, until, finally, a continuous growth takes place. These variations in the growth activity of papillomas have been related by Jonkhoff to the proliferative rhythm of the hairs. The pedunculated and horny warts generally show a persistently benign character, although exposed to continued tarring. The sessile warts display a much higher growth rate than the pedunculated growths, and a distinct tendency toward a malignant transformation. Additional sources of tar cancer are ulcers formed in the bases of papillomas which have fallen off. Some papillary tumors seem to be malignant from the start; but occasionally, cancers develop in a skin which appears to be normal and free from hyperplastic lesions (Guldberg; and Deelman).

Malignant lesions may appear outside the tarred area in environmental, and, apparently, normal and intact skin (Babès and Serbanesco). This phenomenon was observed, by Schürch and Winterstein, in mice and rabbits which had been painted with 3:4-benzpyrene, one of the carcinogenic constituents of tar.

In some exceptional cases the course of events may differ from that just described. The papillomas may fall off leaving a pachydermic, and markedly inflamed skin, which becomes increasingly atrophic without developing any subsequent, malignant growths.

Microscopical Changes. STAGE 1. During the first weeks of tarring, a slight thickening of the epidermis develops associated with an increased keratinization of the superficial layers. Some of the epidermal cells show a minor to moderate degree of vacuolation. The subepidermal, connective tissue contains congested, dilated blood vessels, and exhibits interstitial edema and inflammatory leucocytic exudate. The maximal dilatation of cutaneous capillaries, existing during this phase, represents one of the most striking and characteristic features, and persists in an exaggerated form during the following stage of pachydermia (Itchikawa and Baum; Yamagiwa and Itchikawa; Guldberg; Kreyberg; Dreifuss and Bloch; Möller; Lipschütz; and Döderlein).

STAGE 2. Now, the rather mild, hyperplastic thickening of the epidermis, found during the first stage, becomes more marked, mainly involving the basal and granular layers. The cells composing the epidermis are larger than normal, and assume, in places, an oblong shape because of lateral pressure, which is the result of cellular crowding. The cornified layer is considerably thickened (hyperkeratosis). Similar changes are seen in the epithelial lining of the hair follicles, causing an accumulation of cornified masses in the follicular ducts; and the follicles and adjacent hair roots become dilated and cystic, resulting in an atrophy of the hairs.

While the demarcation between the epidermis and the underlying, connective tissue continues to be sharp and distinct, the epidermal outline has become irregular, through the formation of small, epithelial buds and ramifications projecting into the connective tissue. The capillaries and small veins of the subepidermal tissue are congested, dilated, and, often, ectatic. The corium and subcutaneous connective tissue shows swollen, collagenous fibrils and an increase of elastin. Varying numbers of lymphocytes, plasma cells, eosinophilic leucocytes, and mast cells are found in these tissues, especially, in the perivascular regions.

STAGE 3. The marked hyperplasia of the epithelium of hair follicles, which results in the formation of folliculo-epitheliomas, is the most characteristic development during the early part of the third or neoplastic stage. The follicular epithelium, becoming highly keratotic, proliferates and forms small elevations in the skin, which, later on, assume the character of delicately pedunculated, papillary excrescences. In the base and stalks of these papillomas there is a rich network of dilated, hyperemic, and ectatic capillaries, which are,

in part newly formed. Sometimes, these vascular proliferations are so extensive that the papillomas appear as angio-epitheliomas.

The boundary between the lining epithelium and the connective tissue core is always sharp. No atypical, epithelial cells are found in the keratinized, epithelial lining covering the vascular stalks, in which the endothelium of the delicately walled vessels is, often, contiguous with the epidermal surface layer. Frequently, the mitotic figures are increased in the epithelial coating.

The ectatic vessels, located at the base of the papillomas, are somewhat larger than those present in the stalks. Unless circulatory disturbances exist, neither obliterative, endarteritic processes nor degenerative, endothelial changes are observed in these vessels during the development of neoplastic formations. There is, occasionally, evidence of thrombus formation in the lumina of the angiectases. Any interference with the circulation in the larger afferent or efferent vessels of the papillomata, caused in this manner, is followed by degeneration and necrosis of the tumor, if the circulatory impairment is severe; otherwise, a slowing or arrest of the proliferative activity results in case of milder, circulatory disturbances in these vessels. There is, under such conditions, an absence of mitoses in the epithelium of the upper half of the affected papillomas (Deelman; Kreyberg; and Guldberg). The angiectases observed during this stage are permanent and irreversible sequelae of the tarring.

In addition to pedunculated papillomas, larger, more highly keratinized projections may be formed from keratinized, follicular sacs, which appear as solid, cornified horns on the surface of the skin. Through the conglomeration of epithelial proliferations of several hair follicles and hair sac cysts, broad-based, papillomatous warts may ensue (keratomas). In a manner typical to these reactions, the subjacent connective tissue remains passive, in contrast to the marked and essential participation of these elements in the formation of pedunculated papillomas. Apart from the warty growths, originating from epithelial proliferations of the hair follicles, papillary excrescences may be formed directly through a proliferation of the epidermal cells.

Intrinsic, epithelial proliferations extend from the bottoms of follicular sacs into the surrounding connective tissue, consisting of irregularly shaped, and actively growing cell strands. An increased local growth of the epithelium of sebaceous glands, sometimes assuming adenomatoid character, is always found within the tarred area (Deelman; and Reinhard and Thibaudeau). The corium contains a great abundance of blood vessels, and shows an increase of young, fibroblastic cells (Guldberg; Kreyberg; Ulesco-Stroganova; Deelman; Woglom; and Döderlein). Döderlein called the localized accumulations of ectatic vessels "proliferation centers" of papillomatous formations, as they are considered the foci from which vessels and connective tissue grow beneath into tongue-like, epithelial excrescences, which develop into ramified papillomas.

The development of fibrotic and hyalinized areas in the subepithelial connective tissue is associated with atrophic changes in the overlying epidermis (Ulesco-Stroganova). Inflammatory, leucocytic (often eosinophilic) reactions are usually mild, and located in the connective tissue near the base of benign, neoplastic proliferations, which are free from melanin-containing cells (Leroux). The elastic fibrils of the corium and subcutis exhibit progressive, degenerative changes; while part of the nerve tissue elements are destroyed, and part undergo regenerative proliferation.

In addition to the benign multicentric, primarily multicellular, hyperplastic and neoplastic proliferations, there develop malignant, blastomatous growths which may be derived from various, primary lesions.

Cancers originating through transformation of benign papillomas start as intraepithelial areas of atypical cells, undergoing more rapid proliferation than surrounding parts of the epithelial lining. The cells of such potentially malignant foci possess an unusually large nucleus and a large amount of cytoplasm. Often, localized, multiple, cornified areas appear in the epithelial coat of papillomas with precancerous foci. These are located at the base of papillomatous excrescences, at the bottom of hyperplastic hair sacs, or in the wall of follicular cysts. Sometimes, malignant proliferations appear in the tips of papillae, especially if these are exposed to intense trauma. With progressive growth, the foci of irregularly sized, shaped, arranged, and stained cells show loss of polarity, and penetrate as buds and strands into the underlying, connective tissue of the cores and base, which, usually, show a localized and marked proliferation of blood vessels.

Incipient, central keratinization is noted with the increasing size of the strands and nests. In spite of their morphologically malignant appearance, these epithelial proliferations do not show a marked tendency toward the invasion of lymphatics, blood vessels, and muscle tissue, and the formation of metastases. There exists evidence that some neoplasms which have reached this stage of "histological malignancy" may regress completely, with or without tarring (Ferrari; Maisin; Leroux; and Bonne); while others overcome some restraining and defensive influences of the organism, and, finally, exhibit symptoms of "physiological malignancy" (Maisin). This development may take place after cessation of tarring. Investigations on mice, which had been tarred until small warts were visible, indicate that during the early stage of these neoplastic reactions, the morphological appearance does not reflect the malignant potentialities already present in some of these formations (Leitch).

The great majority of malignant manifestations exhibit the histological features of cornified, squamous-cell carcinomas. The minority possess a certain resemblance to basal-cell cancers, being composed of small cells having a low tendency toward keratinization, and showing a reticular and ramified arrangement. Occasionally, carcinomas displaying a sebaceous gland-like structure are

seen. In addition neoplasms occur, composed of irregular, polymorphous-cell types or of spindle cellular structures, sometimes mixed with squamous cellular elements. These so-called carcinosarcomas grow as compact, crowded, cellular nodes containing little stroma (Deelman; Döderlein; Borst; Guldberg; Woglom; Roussy and Leroux; Guérin; Appelmans; and Bloch and Dreifuss). Some investigators believe that these fusocellular carcinosarcomas are more dedifferentiated types of carcinomas [pseudo-sarcomas (Roussy and Leroux)] than the ordinary varieties; but are less malignant than these (Guldberg), as they do not produce visceral metastases. Others (Appelmans) contend that fusocellular as well as polymorphous cellular varieties of carcinosarcomas frequently produce metastases. These carcinosarcomas after tarring are morphologically identical with neoplasms observed in the skin of rats and mice, after prolonged exposure to solar or ultraviolet rays.

Apart from these malignant epithelial reactions, there occur in the skin of tarred mice and rabbits epithelial proliferative responses, which are of a locally restricted type. They are composed of highly anaplastic, irregularly arranged, and infiltratively growing, epithelial cells. These lesions do not grow to any extent, do not produce metastases, and do regress. These histological expressions of spurious malignancy (Rous and Kidd) are called carcinoids (Borst). They are considered by Rous and Kidd as results of a continued irritation, bringing the tissue into a state of excitability, which may persist long after the skin has become apparently normal. In tar carcinoids the connective tissue may assume a peculiar, mucinoid character, which makes it distinct from the epithelial elements enclosed by it. Similar anaplastic, carcinoid reactions have been described by Hueper in the bladder of dogs, resulting from prolonged and intense exposure to beta-naphthylamine.

The connective tissue underlying malignant manifestations exhibits a progressive degeneration of the elastic fibrils, and is often densely infiltrated with lymphocytes, neutrophilic and eosinophilic leucocytes, and plasma cells. These inflammatory reactions are, in part, the reaction to secondary infections which invade the tissue through the fissured and ulcerated surfaces of the cancers; and, in part, they are responses to the action of irritative substances contained in the tar.

Melanotic neoplasms are, apparently, rare reaction products of the experimental application of tar, as Lipschütz, who observed such sequelae in grey mice, and Passey who obtained melanotic cancers in dogs after tarring, are the only investigators to report their occurrence.

XVI. CAUSATIVE MECHANISM

Tar cancers have been considered for a long time as characteristic examples of and important evidence supporting the chronic irritation theory of cancerigenesis. (Lubarsch; Döderlein; and Yamagiwa). The irritative components

of tar, such as the acridines, were regarded as particularly active in eliciting the neoplastic response. It is correct that the development of malignancy in the skin of man and animals exposed to tar is accompanied, in general, by a marked chronic, inflammatory reaction in the subepidermal connective tissue. But recent, experimental studies of Reinhard and Thibaudeau made on mice, which were subjected to tarring and roentgen-irradiations, showed that tar cancers may develop in the skin without being associated with any appreciable, inflammatory reaction. This observation indicates that a chronic, chemical dermatitis does not have an essential part in carcinogenesis by tar, but is mainly a coincidental phenomenon.

This theory has lost many of its former supporters after the discovery of synthetic carcinogens of the anthracene series, and the experimental demonstration that the chief irritative chemicals contained in tar are noncarcinogenic. Kennaway investigated a large number of substances present in or derived from tar which proved to be noncarcinogenic (ancenaphthene, fluorene, fluoranthrene, dihydroanthracene, hexahydroanthracene, beta-methylanthracene, phenanthrene, retene, pyrene, picene, truxene, naphthacene, naphthanthracene, chrysogene, benzerythrene, crackene, diphenylene oxide, betanaphthofurane, alpha-and-beta-naphthene, alpha-dimethylquinoline, carbazole, phenyl-p-naphthylcarbazole, acridine, diphenylene sulphide, tetraline, naphthalene, naphthoyl benzoic acid, beta-naphthoic acid, dinaphthylene dioxide, beta-dinaphthyl ether, beta-2-tetroyl propionic acid, gamma-2-tetralylbutyric acid, phenylisocrotonic acid, cyclohexane, cyclohexene, styrene, hydrophenanthrene, hydrochrysene, hydroretene, dodecahydrotriphenylene, octhracene, octhracenone, 1.2-benzanthraquinone, 2.3-tetrahydrobenzanthracene, and perylene).

When Kennaway tested 1.2-benzanthracene, he found this substance to be carcinogenic for the skin of mice. This positive observation led him to examine other benzanthracene derivatives of which, during the early stages of this investigation, 1.2.5.6-dibenzanthracene and 1.2.7.8-dibenzanthracene were found to give rise to cancer formation. None of the synthetic, carcinogenic substances discovered at first could be demonstrated in and extracted directly from tar. Nevertheless, an important and effective approach to this problem had been obtained, since Mayneord had found, in 1927, that all carcinogenic fractions obtained from tar were very fluorescent, and possessed a characteristic fluorescence spectrum. By utilizing this information and new methods of identification by fluorescence spectroscopy, Cook succeeded, in 1933 to isolate from tar 3.4-benzpyrene, which was shown to possess definite, carcinogenic properties. Firket and Malter found that English pitch contains 3 per cent 1.2-benzanthracene and 0.3 per cent of 3.4-benzpyrene; German pitch, 1 per cent 1.2-benzanthracene and only traces of 3.4-benzpyrene; Cockerill pitch, 2 per cent 1.2-benzanthracene and 0.2 to 0.3 per cent 3.4-benzpyrene, and Augrée pitch, 8 per cent benzanthracene and 0.3 to 0.4 per cent 3.4-benzpyrene. Before

the successful isolation of specific, carcinogenic chemicals from tar had been accomplished, a number of other possibilities, which may be listed for their historical value, had been considered as the causative factor of tar cancer.

Schamberg assumed that the irritative action of tar upon the skin was due to the presence of radioactive substances in this material. The rays emitted were thought to be responsible for the epithelial proliferations observed. This conception received some support from Kabakjian, who showed that tar exerted a certain effect upon photographic plates. Kabakjian himself, however, ascribed this action of tar to the production of a gaseous material released from the tar. When it soon became apparent that tar did not contain any radioactive material, the hypothesis of Schamberg was discarded.

Lewin (in 1913) pointed out that tar dermatitis was caused by photosensitization of the skin to solar rays by certain substances (acridines, substances belonging to the anthracene and anthraquinone series) contained in tar. Serious consideration was given to the possibility that photodynamic processes and melanin changes produced by them might play a direct or contributory rôle in the development of tar and pitch cancer (Baader; Büngeler; and Lauchs). The most important evidence, supporting the conception of a causal interrelation between tar carcinogenesis and photochemical action, is that fair skinned, blue-eyed, and blond individuals are considerably more susceptible to tar cancer than dark-skinned persons, who are, also, less likely to develop solar cancer (Hunt; Heller; and Koelsch). It might be interesting to connect the accumulation of melanin in the skin, taking place under the influence of tar, with the subsequent development of a cutaneous malignancy, as melanin contains principally aromatic amino compounds, which have some chemical similarity with known carcinogenic agents.

An increased, pathological pigmentation as such cannot be considered as a contributory factor to any kind of carcinogenesis of the skin. Disturbances of this type are observed following physical and chemical irritations of the skin of the most varied kind, without resulting in or favoring the development of skin cancer. Exposure to light is not essential for the production of tar cancers, and pitch and tar cancers are observed frequently in regions of the human skin, which are rarely exposed to light (scrotal sac) (Teutschlaender). Foerster and Schwartz contended that photosensitizing radiations predominate in the short wavelengths of the sun's spectrum chiefly between 3,900 and 5,000 angstrŏms; and that fluorescent spectra emitted by photosensitizing substances contained in tar differed from those involved in the production of tar epitheliomata. These investigators concluded that tar melanosis is the result of a true photosensitization, coming from an exposure to specific, spectral bands, and not a manifestation of a chemical contact sensitization or an allergic reaction (photoallergy). As tar and pitch melanosis usually extend to the nonexposed parts of the skin, such as the scrotal sac, this claim is not entirely correct. Clinical

as well as experimental evidence seems to favor the viewpoint that solar radiation accelerates the development of tar and pitch cancers, but is not an essential factor (Büngeler).

Bayet advanced the theory that arsenic in tar was the actual carcinogenic agent. As tar cancers and arsenic cancers of the skin exhibit a different type of local distribution, and as the relative content of arsenic in various types of tar has no relation to the carcinogenic potency, this theory was abandoned. Recently Hammett proposed, in connection with his hypothesis of the sulfhydryl action on the induction of benign and malignant cell proliferation, that carcinogenic action of tars was attributable to their content of mercaptans and sulfides, which were said to promote the regenerative processes beyond repair. Subsequent observations of Hammett and Reimann have demonstrated that sulfhydryl substances neutralize the action of chemical carcinogens. Hueper has pointed out that the factual basis for Hammett's theory was defective, and contrary to well-established, biological observations on the nature of growth-promoting factors. Consequently, this theory has not found any supporters. Bloch has noted already that the carcinogenic constituents of tar do not contain nitrogen, sulfur, or arsenic.

The most recent hypothesis as to the causative mechanism of tar cancer has been elaborated by Rous. He contended that tar papillomas proper produced in rabbits are so different from other responses to tar, that they imply the action of a differing, specific cause (virus), especially since these neoplasms resemble morphologically those produced by the papilloma virus in rabbits.

These conceptions are based upon the following evidence. When the papilloma virus (Shope) was injected intravenously into rabbits whose ears had been tarred previously for 1.5 to 3 months, there developed rapidly a large number of papillomas and a few squamous-cell carcinomas in the tarred area. The tarred ears of control rabbits, which had been tarred only, showed merely warts, which receded spontaneously later. The investigators concluded that the virus activated the tar warts, determined the site of the papillomatous responses, and intensified the neoplastic results of tarring by causing the development of a great variety of benign and malignant tumors.

Rous and Kidd claimed that different types of cellular changes observed are produced by an action of tar upon epidermal cells, and do not reflect differences in the potentialities of the virus. This is because the neoplasms in tarred animals develop from focal or punctate, cellular anomalies, the biological character of which is fixed from the start. Rous has advanced from these and other observations the hypothesis, that tar activates a carcinogenic virus, previously present in a dormant state in the cells with which tar may come in contact. Thus, an ubiquitary virus represents the general, direct cause of tar cancer, while the chemical agent determines only the time and site of the activity of the virus. While such speculations are interesting and thought-

provoking, the available evidence does not suggest that such an etiological mechanism is operative in the development of occupational tar and pitch cancers.

The histological changes described, which precede the formation of benign and malignant tar and pitch tumors, preclude the possibility that these neoplasms are of dysontogenetic origin, of embryonic cell rests, or congenital tissue malformations, as expressed by the Cohnheim theory of cancerigenesis. Kimla suggested that chronic, proliferative stimulation exerted by tar upon the epidermis created an allergic status. Consequently, tar cancer might be regarded as the local and multicentric growth manifestation induced by the production of a permanent, allergic, proliferative stimulus.

Warburg's theory of cancerigenesis announced that cancer resulted from the presence of a local oxygen deficiency of cells, causing the development of cells possessing a marked, anaerobic, glycolytic metabolism. Kreyberg, pointing to this theory, asserted that conditions existing in the tarred skin at various periods favored the production of such cellular, metabolic changes, and, thereby, the creation of malignant cells. Kreyberg stated that hyperplastic lesions in the tarred skin occurred when an extraordinary degree of hyperemia and an abundant, cellular, nutritional state existed. Malignant transformation of these manifestations appeared when severe, circulatory disturbances had ensued in the underlying, vascular tissue, interfering with adequate oxygen supply of the epidermal cells.

Similar claims were made by Orr, who studied the cutaneous changes produced in the skin of mice through repeated applications of 3.4-benzpyrene, the carcinogenic chemical isolated from tar. He contended that cancer developed in the skin of these animals on the basis of a chronic, passive congestion of connective tissue. This is caused by the development of fibrous scars in the deeper connective tissue, and interferes with the proper nutrition of overlying, epidermal cells. Some support for these assertions was supplied by the results of metabolic studies conducted by d'Allessandro and Büngeler. They observed that the tissues of various organs of tarred mice possessed an increased glycolytic metabolism.

A conception, opposing in many respects that advanced by Kreyberg, was propounded by Guldberg; and Ulesco-Stroganova. Commenting upon the observations made by Kreyberg, concerning the appearance of intravascular hyalinized thrombi at the time of the epithelial cancerization, Guldberg stated that these formations were actually artefacts. This investigator emphasized, in contrast to Kreyberg, the necessity of proliferative and dilatatory, vascular reactions as prerequisites for epithelial growth. This condition was stressed previously by Itchikawa and Baum in relation to the development of tar cancer. Reference was made by Guldberg to a statement of Virchow asserting that hyperemia and dilatation of blood vessels always accompany cellular regeneration and proliferation, although they cannot occasion such processes.

Guldberg's own observations and those made by Ulesco-Stroganova revealed the actual existence of vascular proliferation, dilatation, and hyperemia in the tarred skin of mice, which provide an increased blood supply to the growing cells. Ulesco-Stroganova noted that tar cancer cannot develop unless the connective tissue remains reactive and capable of vascular newformation. In the absence of such vascular and circulatory responses, fibrosis and epithelial atrophy results. The development of cancerous manifestations does not follow, because cancerous proliferations do not ensue on the basis of an atrophic tissue.

Observations made by Itchikawa and Kotzareff, and confirmed by Rémond, Bernardbeig, and Sendrail, support these contentions. These investigators noted a retardation and impairment of the cancerous responses to tarring in the ears of rabbits when the anterior and posterior auricular nerves were resected. Malignant lesions developed more quickly after the extirpation of the cervical sympathetic ganglions, an operation which caused a prolonged dilatation and hyperemia of the auricular blood vessels and an improved, blood supply to the tarred ear. The data presented suggest that cancerization of the epithelial cells by tar, i.e., the fundamental change in the biological character of these cells, is entirely independent of the alterations which the vessels may undergo in the tarred skin. In spite of this, the presence or absence, as well as the persistence or regression of these vascular manifestations, exert a decisive influence upon the localization, proliferative speed, and ultimate course of the ensuing, neoplastic reactions.

XVII. TECHNICAL, SANITARY, AND MEDICAL PROTECTIVE AND PRECAUTIONARY MEASURES

Technical measures aimed at the prevention of tar and pitch cancer must be directed toward the elimination or, toward the greatest possible reduction of the degree, duration, and frequency of contact with these substances. In general, the high temperature combustion products of coal and oil possess the highest, carcinogenic potency. In view of this, it appears essential to introduce, wherever possible, low temperature carbonization and distillation processes in order to obtain a product of low, carcinogenic potency. The replacement of horizontal retorts by vertical retorts in gas works constitutes a definite and effective improvement.

If the production of high carcinogenic tar and pitch cannot be avoided, care should be taken that these products are used, in such a way and for such purposes as require as little handling and entail as little contact with the human skin as possible. Sladden requested the substitution of carcinogenic pitch used in the English patent fuel industry by some suitable, noncarcinogenic material. Such a replacement has been made in briquette manufacturing in the United States, according to Heller, as petroleum-asphalt pitch is used in place of coal-tar pitch. An additional reduction of the carcinogenic hazard, which is particularly essential whenever carcinogenically potent tar or pitch is used,

is obtained by closed production methods, the installation of exhaust ventilation, and means tending to decrease or to eliminate the formation of excessive amounts of dust, such as the wetting of pitch. A typical example of this type of technical improvement, which has resulted in a marked drop in the incidence of pitch cancer, is represented by the Fohr-Kleinschmidt method in the briquette industry (Teutschlaender; Brenner; Grempe; Lehmann; and Heller).

Reports concerning the occurrence of pitch cancer in the corkstone industry of several countries indicate that marked changes in machinery and in sanitary measures appear to be urgently needed (Barkmeyer; Schürch and Schrafl; and Lauchs). Schürch and Schrafl mentioned that no protective measures or technical precautions are observed in Swiss operations of this type; and the workers employed in these plants are kept uninformed concerning the serious, occupational hazard they are exposed to. Similar unfavorable working conditions seem to exist in certain factories producing roofing paper and dry battery cases. It is important that industrial engineers devise proper machinery for those operations, in which contact with carcinogenic material cannot be avoided, if the work is executed by hand.

Apart from measures of technical nature, an effective control of occupational cancers requires the introduction and rigid enforcement of certain regulations concerning personal hygiene to be observed by the workers employed in work entailing contact with tar and pitch. Workers engaged in such occupations out-of-doors should wear hats with wide brims whenever the sun is shining brightly, that is, during the summer, and during the winter, when snow on the ground reflects the solar rays. If such work is carried on in sunny climates, it may be necessary to conduct such activities during the night exclusively, to avoid the production of a tar dermatitis on a photodynamic basis. Clothes worn by workers should be loose-fitting and should not cause friction, particularly around the scrotal region. Provisions should be made for adequate locker space, where the workers can change from street clothes into frequently cleaned working clothes. Bathing facilities with warm showers should be provided and baths should be taken daily at the end of the shift by the workers. They should be urged to clean their hands carefully before urination so as to avoid any soiling of the penis and scrotum with tar during this act. The cleaning of hands soiled with tar or pitch with the aid of grease or oil, a procedure widely practised, is not always safe, unless these cleansing agents are completely removed, because the grease or oil used for such purposes may possess carcinogenic properties (Barkmeyer; and Teutschlaender). Pitch workers should not have moustaches as the pitch dust settles between the hairs, causing a dermatitis, which induces the workers to scratch and rub, thus helping in propagating a neoplastic response. The observation of these rules of personal cleanliness by the workers should be strictly supervised, and infrac-

tions on the regulations should be punished, if necessary, by removal of the worker from the operation. Plant managers, foremen, and workers should be adequately informed by special instructions (lectures and films) as to the nature of the hazard, the symptoms produced, and the technical and sanitary, precautionary and preventive measures to be taken and observed. Signs and posters with the essential information should be displayed in working rooms and wash rooms, where they can be easily seen and read.

Barkmeyer, Somerford, and Teutschlaender proposed the following rules for and during the employment of individuals in tar and pitch operations:

1) Persons with skin diseases (xeroderma pigmentosum, ichthyosis, and hypersensitivity to tar or related substances) or previous, appreciable, occupational exposure to tar and pitch, entailing the existence of a sensitization of an unknown degree, should not be employed.

2) Young, mentally alert, and clean men appear to be the best-suited for this work, and should be given preference in employment.

3) There should be a time limitation for the duration of employment in this type of work (2 to 3 years). At the end of such a period the workers should be shifted to a work which does not involve any contact with tar or pitch.

4) Men who appear to be unable to follow the precautionary and sanitary directions given should be eliminated from such work.

5) Workers should be subjected to periodical, medical examinations (3 to 4 months), so that cutaneous lesions can be discovered before they become malignant.

6) Workers should report any suggestive skin manifestations to their physician. They should, definitely, not rub or scratch any such skin lesions and, especially, not indulge in any self-treatment, that is, the removal of warts and papillomas by the application of acids, or by mechanical force.

7) Workers should be provided with agents for the protection of the skin against direct contact with tar and pitch. The use of a moist clay for the covering of the face and forearms, customary in some factories as a cheap method of protection, must be considered as unsatisfactory, as the clay dries and falls off easily, especially from those parts subjected to movement. Ointments appear to be more effective for this purpose. The ointments used should be applied to all vulnerable locations, i.e., sites where direct contact exists, where perspiration is abundant (axillary and inguinal regions), and where friction from clothing occurs [especially scrotum and places where spectacles may rub against the skin (eyebrows, bridge of nose, and temples)]. In addition to Nivea Creme the following ointments have been recommended (Lehmann; and Foerster and Schwartz):

Rp. Zinc oxide	
Talcum venet,	aa 100 gm.
Glycerin	
Aqua dist.	aa 200 cc.

Rp. Quinine hydrochloride	0.02 parts
Stearic acid	2.9
Wool fat	8.0
Liquid petrolatum	5.0
Triethanolamine	0.38
Ethyldiethylene glycol	1.0
Distilled water	10.0

8) Workers should wear undergarments for protection against dust, especially concerning its contact with the scrotum. Supervision should be exercised so that the genital region is kept clean and adequately washed.

9) Spectacles for the protection of the eyes should be worn only when rims are covered by felt, which must be kept clean.

10) Bearers of ulcerative and cancerous lesions should be removed permanently from any future contact with pitch, tar, or related substances, such as creosote, anthracene oil, and crude lubricating oil. The return of workers with cured tar or pitch cancers to their former occupation aggravates considerably their prospects of a lasting cure. The skin of such individuals responds more readily with the development of additional, malignant growths upon further contact with these agents, than a normal skin. Tarred skin contains numerous, potentially malignant foci, which are activated by a continued exposure to the offending agent.

11) Post-mortem examinations should be performed on all tar and pitch workers (occupied, former, and retired) whether or not they showed any cutaneous malignant lesion during their lifetime. It is important to establish definitely if occupational exposure to tar and pitch brings about an excessive susceptibility to cancers of organs (lungs, gastro-intestinal tract, liver, and urinary bladder) other than the skin.

XVIII. THERAPY

Foerster and Schwartz recommended that pitch dermatitis be treated, during the working hours, with protective and sedative lotions containing ichthammol and zinc oxide, and that soothing emulsions be used during the night. Tar or pitch burns, when superficial and covered by a crust formed by the fixation of the tissues with tar or pitch, may be permitted to remain without any protective dressing. A 5 per cent tannic acid solution may be applied, if no fixation of the tarry substances on the surface has occurred. Butesin picrate dressing is an efficacious, therapeutic measure in such cases. Deep burns, on the other hand, have to be cleaned thoroughly, and any tarry matter contained in them has to be removed carefully, to prevent any subsequent inclusions of traces of this material in the granulation tissue and in the subsequent scar. Wet dressings are best for keeping the wound open and for affording proper and free drainage.

Tar and pitch warts may be removed by cold cautery or by the application of carbon dioxide snow. Recent observations made in England have shown that pitch warts are highly sensitive to radium, which may be applied, unscreened, in flat applicators containing 5 mgm. per centimeter. These applicators are kept in contact with the wart for periods of 80 to 100 minutes. The warts disappear generally within four or five weeks. Malignant lesions may be treated with roentgen- or radium rays, surgical excision, or electric cautery, depending upon the location and extent of a given tumor.

XIX. MEDICO-LEGAL ASPECTS

Pitch and tar epithelioma is recognized as a compensable occupational disease in a great number of countries and states (England, France, Germany,

Switzerland, Holland, Italy, Russia, Australia, New Jersey, New York, Pennsylvania, Illinois, Massachusetts, and Wisconsin). In 1935 laws were enforced in Germany which regulated the character and extent of technical precautions, and the engineering aspects of production methods to be used in the briquette industry. This law forbids the further employment of persons with pitch cancer in such operations, and prevents the re-employment of men who were once affected by but cured of this industrial neoplasm. Provision has been made that such workers, who have sustained these occupational injuries and are handicapped in making their living, receive a temporary compensation, until they are trained for some other type of work and have secured employment.

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c. Fractionation and Distillation Products of Mineral Oils, Oil Shales, Lignite, and Coal Tar (Processed Oils and Paraffins)

I. CHEMICAL AND TECHNOLOGICAL ASPECTS

Semi-refined and refined oils and paraffins are products of the fractionation and distillation of petroleum, oil shales, lignite, coal tar, and of the cracking of coal. Their chemical composition depends upon and varies with the original substances they are prepared from, and with the methods by which they are obtained (refining processes).

Petroleum Oils. Crude mineral oil is separated into several fractions by distillation at various temperatures. The volatile gasoline is driven out of the crude mineral oil at a temperature ranging from 90°C to 200°C. The next fraction, kerosene, is obtained when the contents of the still are heated to approximately 250°C. The residue is subjected to a temperature up to 300°C. gas oil is distilled off. What is left at the bottom of the still, represent-

ing about 36 per cent of the original crude mineral oil, is used without further processing as fuel oil, or is heated to a high temperature, until the wax distillate comes off, which contains lubricating oil and wax. Through the use of special separation methods, involving the application of refrigeration to the distillate, the wax is extracted from it and a crude lubricating oil is obtained from the wax presses. This crude lubricating oil is then redistilled, fractionated into light and heavy fractions, treated with sulfuric acid for the removal of undesirable impurities, and filtered through Fuller's earth for the removal of colored contaminations. Additional amounts of heavy lubricating oil are obtained by subjecting the residue left in the still to various treatments with chemicals, until the waxy constituents and the lubricating oils are separated with the help of centrifugal separators. Through these successive steps of fractionation, crude mineral oils are divided into gaseous and liquid paraffins; olefins and poly-olefins (which are fractionated into gaseous and liquid paraffins, naphthenes, and lubricating oils; while the crude naphthenes are split into paraffins, naphthenes, and lubricating oils with reduced hydrogen content); and solid paraffins (which are fractionated into liquid paraffins, olefins, and lubricating oils). The naphthenes are cyclo-paraffins (cyclohexanes-cyclohydrobenzols; five and seven member ring compounds), some of which are unsaturated, cyclic compounds (anthracenes, naphthalenes, and phenanthrenes). The high boiling hydrocarbons of this group are polynaphthalenes, aliphatic and cyclic unsaturated hydrocarbons (Gruse; and Lewkowitsch).

During the refining process the oils are treated with sulfuric acid, which later is neutralized by bleaching with caustic soda, and are subjected to intermediate washings. This processing has the following effects upon the oils: 1. precipitation or solution of sulfur compounds, resins, and petroleum acids; 2. combination of acid with nitrogen bases and some unsaturated hydrocarbons; 3. polymerization of unsaturated hydrocarbons; 4. sulfonation of aromatic hydrocarbons; 5. oxidation of some unstable hydrocarbons; 6. hydrolysis of olefins and polymerization of olefins; and 7. removal of unsaturated hydrocarbons (diolefins and acetylene), or their conversion into more stable forms (Heller). During the distillation process at high temperatures, aromatic substances (anthracenes and phenanthrenes) are generated from aliphatic ones originally present in the crude oil. It is for this reason that distillation products may display biologic properties different from those exhibited by the raw material. Crude Californian oils have been found to be noncarcinogenic, while some of their products of fractionation and refining were shown to possess carcinogenic qualities (Twort).

Shale Oils. The distillation of oil from oil-bearing shales, which are hard, black, non-crystalline rocks resembling in appearance pitch, started around 1850 in the West Lothian district of Scotland. Up to that time vegetable and animalic oils had been used exclusively for the lubrication of the machinery

in industrial and, especially, textile establishments in this region. The shale was roasted originally in high temperature horizontal retorts, which since 1868 have been replaced by vertical retorts. The fumes generated in the retorts are condensed, forming a dark, viscid fluid, from which ammonia liquor and crude oil are separated by gravitation (Leitch; and Ross). The crude oil is heated from 510°C to 704°C in a still. Steam is blown through it, resulting in the production of the so-called "green oil", which is a dark, thick, viscid fluid. It contains paraffins, olefins, naphthenes, benzenes, toluol, xylol, quinolines, chrysene, phenols, alpha- and beta-cresol, xylenols, pyrocatechin, pyridine, and sulfur compounds. The "green oil" is treated with 2 per cent sulfuric acid and, afterwards in another vessel with 1 per cent caustic soda. The "green oil" is re-distilled with steam, and fractionated into light oil, intermediate oil, and heavy oil. The light oil, after being treated with sulfuric acid and caustic soda, is distilled again, and fractionated into "burning oil" and a second fraction of "intermediate oil". The heavy oil which contains the paraffin is passed through pipes to the cooling sheds. It is here pumped through ammonia freezers which cool the oil to minus 14°C, at which temperature the paraffin solidifies and separates from the oil. This mixture of oil and paraffin scale is then sent through filter presses, in which the oily parts are expressed, leaving a sludge or scale. The heavy oil (blue oil) thus obtained is treated again with sulfuric acid and soda, distilled, and fractionated into intermediate oil and lubricating oil. All intermediate oil and lubricating oil fractions are passed through freezers for the removal of paraffinic admixtures, which have remained in the oily fraction, and then sent through hydraulic filter presses. These semi-refined oils are processed further for the production of more refined oils, such as unfinished gas oils, cleaning oils, and lubricating oils.

Lignite Oils. The carbonization of lignite takes place in generators, which are brick cylinders with a grate at the bottom through which air and steam is forced through the burning lignite which fills the lumen of these vessels. The heat generated in the lower part of the generator causes the development of tar fumes from the lignite present in the upper portion. The fumes are condensed to an oily tar, which is distilled, and fractionated into three main fractions. The first fraction which is free paraffin represents about one-third of the tar. The second fraction recovered contains oils and low melting paraffins; and the third fraction consists, in part, of hard paraffins. The two paraffin-containing fractions are treated like the heavy oil fraction obtained from crude shale oil. They are subjected to refrigeration in rotating coolers, where the paraffin crystallizes and separates from the oily parts, which are expressed in filter presses. The crude oils thus obtained are treated with sulfuric acid and sodium hydroxide and re-distilled. Lignite tar yields, through these procedures, approximately 55 per cent oil. One per cent of this oil is the so-called "solar oil" which is used as a solvent and extracting agent. It is the

lightest fraction following the separation of benzine. 1.5 per cent of the total oils is represented by "yellow oil", employed as fuel in Diesel engines. More than 50 per cent is gas oil used for the production of oil gas, in the manufacture of grease, as fuel of Diesel engines, fuel oil in furnaces, as a lubricating agent, and as an admixture of asphalt. The various lubricating oils obtained from petroleum, shale oils, and lignite oils are further processed depending upon their physical-chemical properties and upon the purpose for which they are intended. They are, thus, converted into spindle oils, cylinder oils, light and heavy machine oils, motor oils, and transformer oils.

Coal Tar Oils. Coal tar oils are obtained by the distillation of tar, distilling over at a temperature from 150°C to 400°C, and represent approximately 65 per cent of the tar. They are composed of paraffins, naphthenes, and olefins with minor admixtures of methylated naphthalenes, anthrazenes, phenols, and creosotes, i.e., substances which are present in crude, but not in purified naphtha oils.

Paraffins. Paraffin is manufactured from the distillation residue of certain mineral oils (Galician and American), from the heavy oil fraction of crude shale oils, and from the paraffinic fractions of lignite. The technical procedures used are fundamentally alike regardless of the nature of the raw material. The distillates containing the hot wax are piped from the stills into the paraffin or cooling sheds, as the extraction plants are called. They are allowed to cool and settle thoroughly before they are pumped into the refrigerators, where they are chilled until they form a solid mass. This frozen material, containing the crystalline paraffin mixed with oily constituents, is scraped off the refrigeration coils with knife-like tools and is transported by a worm screw conveyer into filter-presses. The heavy oil is expressed, leaving a residue of crude paraffin, known as sludge, upon the canvas filters covering the plates of the hydraulic presses. In old type presses workers shovelled the scale upon canvas cloths, which were laid in layers on bogies, the ends and sides of the cloths being folded over, and the pile was placed under the press. The slack wax remaining in the press is scraped off the filter cloths with spade-like tools, and then subjected to refining and purification procedures, to remove coloring matter and small amounts of oil still adhering to the paraffin crystals.

In an older and now generally discontinued method, the paraffin was dissolved in benzine. This solution was chilled and sent through a filter press. After repeating this procedure several times, the traces of benzine remaining in the paraffin were removed by passing overheated steam under vacuum into the purified paraffin, driving the benzine out. The woolen cloths used in the presses were cleaned by hand. In more recent times, the separation of the paraffin from the benzine is accomplished in high-speed centrifuges of the Sharples' type. This process has been replaced in modern plants by the "sweating process". The paraffin scale is removed from the filter cloths by instruments

and the paraffin remaining on the cloths is shaken off by hand. They are placed in a melting pot from where the paraffin is passed into shallow trays with wire bottoms. These trays are exposed in the sweating house to fractionated heating. First, the substances with a low melting point, i.e., the oily impurities, are liquified, run through the nets, and are removed. By gradually increasing the temperature in the sweat house paraffins of different melting points are isolated. These sweating procedures are repeated when necessary. The purified paraffin is filtered through charcoal or recently ignited bauxite for the removal of colored impurities. The finished product is colorless and odorless (Ullmann; Ehrlich; Heller; Ross; Wood; Davis; and Leitch).

Paraffin is used in a more or less purified form in the manufacture of candles, floor wax, paper, shoe polish, skin creams, tooth paste, laxatives, ointments, leather wax, liquid polish, and carbon paper; for the impregnation of matches, soles, threads, and ship cables; for water proofing of wood, brick walls, wrapping paper, food stuffs (cheese), and ammunition (shell cases and cartridges); for the rust proofing of iron pipes; for the protection of ship bottoms against corrosion and worms; as an insulation lacquer in electrotechnical appliances; in oil baths of laboratories; in the hardening of steel; for the paraffinizing of forms in the ceramic industry; as a spray in the rapid drying of printing ink; as a protective agent in the galvanoplastic industry; and as grease for cables.

II. CARCINOGENIC PROPERTIES OF OILS AND PARAFFINS

Clinico-statistical and experimental data show that marked differences exist in the carcinogenic potency of semi-refined and refined oils and paraffins, depending, in part, upon the chemical composition of the raw material, and, in part, upon the method of fractionation, distillation, and refining. By comparison, however, all oils are, in general, less carcinogenic than most samples of gas works tar (Leitch; Schabad; and Twort and Ing). Among the oils, shale oils are usually more carcinogenic than any of the petroleum oils (Leitch; and Twort). Tar oils, which are chemically similar to some crude mineral oils, are more carcinogenic than purified naphtha oils (Strater). While medium heavy oils are the most carcinogenic, Twort found lighter spindle oils, such as those used in the textile industry, of higher carcinogenic potency than the heavier oils employed for the lubrication of engines. Spindle oils are more carcinogenic than transformer or motor oils. Twort demonstrated that fresh motor oil exhibits a lower carcinogenic property than used and, therefore, heated motor oil. Highly refined oils are less carcinogenic than less purified oils (Heller). This does not apply, however, to refined Scottish shale oils, which are highly carcinogenic. Although pure, medicinal, mineral oil has been proven non-carcinogenic (Wood; and Twort), it acquires this quality after being autoclaved at 380°C under 50 atmospheres of pressure (Twort). While some of the semi-refined shale oils, such as unfinished gas oil, cleaning oil, and lubri-

cating oil, have not exerted any carcinogenic action in man, they caused epitheliomas in the skin of mice (Leitch). Lighter Diesel oil was found by Twort and Twort to be noncarcinogenic to the skin of mice; but heavier grade oils were definitely carcinogenic. The oil recovered from the exhaust of a Diesel engine by the extraction of the soot removed from the combustion chamber, was shown, by the same investigators, to be highly carcinogenic. This indicated the possibility of the existence of a not fully appreciated and increasingly frequent source of occupational and nonoccupational cancerigenesis, in view of the constantly expanding use of high-compression, internal-combustion engines of the Diesel type replacing low-compression, gasoline engines. Twort demonstrated that originally noncarcinogenic oils can be converted into carcinogenic ones by the process of cracking (such as occurs during high-compression and high-temperature internal combustion of the oils in Diesel engines). Likewise, primarily noncarcinogenic, crude Californian oil was shown to be carcinogenic after fractionation and distillation (Twort and Ing).

The degree of carcinogenic potency varies with the different fractions. The heavier oils are, in general, more carcinogenic than the lighter oils, which distil over at lower temperature. In shale oils the carcinogenic substances seem to be more predominant in the fractions distilling at lower temperatures, than in those obtained at higher temperatures. This apparently paradoxical behaviour is attributable to the fact that heavier oils are refined with a higher percentage of sulfuric acid than lighter oils. Experience has shown that the treatment of a mineral oil with sulfuric acid lowers its carcinogenic potency.

Differences in carcinogenic potency of various naphtha oils depend upon the chemical character of the crude oil, which, in turn, varies with the field of origin. Among petroleum oils the highest degree of carcinogenicity is exhibited by oils from Venezuela and Borneo; a midway degree of activity is displayed by those obtained from crude oils coming from California, Mid-Continental fields, Rumania, and Mexico; and a low potency is shown by oils from wells of Texas, Pennsylvania, and Russia (Twort and Twort), according to experimental results on mice. These investigators noted that refined Texas oils did not produce any skin tumors in mice, although other refined American oils caused the development of epitheliomas after a prolonged application (40 to 56 weeks), being still twelve times less potent than shale oils (17 to 26 weeks). Twort and Twort deduced from these experimental data that a worker in contact with Pennsylvanian oil is 50 times less liable to develop skin cancer than a worker exposed to shale oil. Thus, refined oils produced from crude oils with a high content of aromatic compounds appear to possess the highest carcinogenic potency.

In general, these experimental observations are in agreement with clinicostatistical findings made among the workers employed in oil refineries of different countries. Ullmann reported the occurrence of skin cancers among

workers employed in Galician and Rumanian fields, while none were seen among men working in Russian fields near Baku. Kolesnikow recorded the development of benign papillomas on the hands and arms of workers employed in the naphtha industry near Grozny in Russia. More recent information, received from Galician and Rumanian refineries (Baader), suggests that such neoplastic, malignant complications have become nonexistent, as Jovin had not seen a single case of oil cancer during the last twenty years among approximately 2,000 workers employed in the four largest Rumanian refineries. Carozzi reported the relatively small number of paraffin and oil cancers among workers in petroleum refineries of France, Germany, Bohemia, Slovakia, Hungary, and Galicia. Wood investigated this question in the chief centers of the Pennsylvanian oil industry, and found, within a period of 6 years, that there were only 4 skin cancers among a total of 124 cancer cases in oil workers. Heller, who studied this problem several years later, noted that not a single case of skin cancer appeared among 1,500 workers employed in 15 oil refineries in Pennsylvania; while 21 cases of paraffin and oil cancer were observed among workers engaged in refineries in New England, New Jersey, and Indiana, where crude oils having an asphalt or mixed base, and coming from southern Texas, Mexico, Venezuela, and Louisiana were processed.

Twort and Twort, as well as Lyth, attempted to estimate the prospective, carcinogenic potency of a particular oil by a determination and evaluation of a number of factors: (*a*) country of origin and region of oil field; (*b*) specific gravity; (*c*) index of refraction; (*d*) fluorescence; (*e*) color; (*f*) viscosity; (*g*) degree of saturation and hydrogenation; and (*h*) iodine value. From a study of these factors in their relation to the degree of carcinogenic potency displayed by various oils tested, the following conclusions were reached:

a) Specific gravity: The carcinogenic potency increases with the specific gravity of an oil. Spindle oils are, therefore, more carcinogenic than motor and transformer oils, while medium heavy oils show the highest grade of carcinogenic power. The blending of an oil, possessing a low specific gravity, with shale oils may cause a marked increase of the carcinogenic potency, without causing any appreciable change in the specific gravity of a given oil. Other exceptions are Texan oils, which have a high specific gravity, and a low carcinogenic potency, this relation being reversed with shale oils.

Since carcinogenic qualities of an oil depend upon the presence and amount of isocyclic compounds, which increase the refractivity index of an oil, a high refractivity index suggests a high degree of carcinogenic potency. Oils with a refractivity index of less than 5,500 are noncarcinogenic and nontoxic, while those with an index above 5,600 are highly toxic and carcinogenic (shale oils) (Lyth). Pennsylvania oils are exceptions to this rule. They are less carcinogenic than Russian oils although they have a refractivity index which is higher than that of the latter. The reliability of information given by the refractivity index is increased with the purity of the oil.

While specific gravity alone gives confusing information, it is of value, in combination with the refractivity index, in judging the prospective, carcinogenic properties of an oil. The following tabulation of the refractivity indices and specific gravities of various oils illustrates this point (Twort and Lyth):

Origin	Refractivity		Specific Gravity
	Means	Extremes	
Russian	5503	5500–5506	9055
Texas	5510	5507–5517	9242
Californian	5540	5537–5543	9317
Pennsylvanian	5546	5542–5552	8901
Mexican	5549	5544–5555	9084
Borneo	5560	5535–5617	9454
Midcontinental	5561	5555–5566	9125
Persian	5565	5563–5569	9046
Rumanian	5570	5568–5573	9276
Shale	5621	5613–5633	8987
Venezuelan	5558	5552–5563	9292

c) Fluorescence: The degree of carcinogenicity of an oil increases with its intensity of fluorescence. Blue fluorescence is more indicative of a high carcinogenic potency than green fluorescence.

d) Color: All colored oils must be viewed with suspicion in regard to carcinogenic potency. Colorless mineral oils are harmless.

e) Viscosity: The viscosity alone gives little information concerning the carcinogenic potency of a particular oil. However, viscosity and refractivity index together may be of value in this respect. Other things being equal, the lower the refractivity index and the higher the viscosity of a refined textile oil, the lower is its carcinogenic quality. While studying a range of commercial distillates of a topped, crude, liquid petroleum from Borneo, Twort and Lyth found that the peak of carcinogenicity was present in a fraction having a viscosity of 200 to 250 centipoises at 25°C.

f) Degree of Saturation and Hydrogenation: Saturated, well-hydrogenated oils are less dangerous than unsaturated, less-hydrogenated oils. Cheaper oils of the same specific gravity, flash, and viscosity as higher priced oils are, usually, less hydrogenated and more carcinogenic than the corresponding, more expensive oils.

g) Iodine Value: The higher the iodine value, the higher the carcinogenic potency of an oil, but the iodine value is only reliable, provided that the oil tested has not been processed. The iodine value of shale oil is 46.2, while that of Russian oil is 15.0.

Twort and Lyth concluded that an investigation of the physico-chemical properties of a given oil renders reliable information, concerning the degree of potential, carcinogenic hazard connected with its industrial use.

III. OCCUPATIONS WITH EXPOSURE TO OILS AND PARAFFINS

Oils. The rapid industrialization of all countries, causing replacement of power generated by man and animals with machine power, which requires oils and greases for lubrication and fuel, has widened greatly the circle of potentially hazardous occupations and has increased enormously the number of workers exposed to these substances with known, but usually low, carcinogenic activity. Oil cancers have been recorded in the following types of workers having occupational contact with lubricating and fuel oils and greases: workers in oil refineries (stillmen, retortmen, still cleaners, oil pumpmen), cotton mule spinners, textile workers, weavers, mechanics, machinists, oilers, greasers, metal grinders, metal lathe workers, grinders of optical lenses, gun smiths, stove cleaners, riggers, and automatic machine operators (Kennaway; Oppenheim; Sharp; Leonardo; Heller; Lambret; Derville and Guermonprez; Haagensen; O'Donovan; Wise; Brockbank and Stopford; and Bridge and Henry).

The most exposed workers in oil refineries are the attendants of the still and retorts, especially, if they clean this machinery, too. Derville and Guermonprez noted that these cleaners enter the hot vessels about three to five hours after the fires have been extinguished, and remove the oily residues and coke-like sludge, which has to be scraped from the walls. The workers are lightly clad during this work. Their skin is exposed to hot fumes, vapors, and oily material which impregnates their scanty clothes. Exposure to carcinogenic material is aggravated, if personal cleanliness is disregarded. The hazard existing in modern oil refineries is very much reduced, as the various processes are carried out in a closed system.

The use of highly carcinogenic shale oils and the presence of special, occupational conditions combine to make mule spinners in England the largest occupational group with oil cancer. Bridge and Henry gave the following description of the spinning machinery, its operation, and the working conditions causing the occupational contact with carcinogenic shale oil used for lubrication: The mule is a machine, approximately 120 feet long, travelling on carriage wheels placed at a distance of 12 feet apart, and running in and out for 64 inches at a speed of from 3 to 4 times a minute. Behind the mule is what is known as a creel, containing the bobbins which supply the necessary cotton for the production of the yarn. Between the creels and mule are the lines of rollers which draft the cotton from the creels into the yarn of the fineness desired, and the yarn, in turn, is wound onto the spindles. The spindles, approximately 18 inches long, are placed at intervals of 1 and 1/5 inch to 1 and 3/5 inch, and run at a calculated speed of from 8,000 to 11,000 revolutions a minute. They are oiled at the footstep once or twice a week, and at the bolster, which is about 8 inches from the top of the spindle and approxi-

mately 2 feet and 6 inches above the floor, twice a day. The oiling of the bolster is done when the mule is at a standstill. In the course of the spinning the mule operative works in the space in front of the carriage, passing backwards and forwards as it moves in and out. During this work and especially when a torn thread has to be pieced the spinners have to lean over, which is a frequent occurrence (at an average 240 times per hour). The scrotal region comes in contact thereby with the faller shaft causing thus a rapid intermittent friction of his trousers with the skin of the region of the groin. The temperature in the spinning room is high, varying between 70° to 90°F, while the humidity is between 60 to 62 per cent.

The spinners are clad in a shirt and a thin pair of cotton or linen trousers, in former years, of a soft, white material, but which have been replaced steadily, since 1905 by blue overalls, made of a hard and coarse material and held by an inelastic brace. The English spinners do not wear undergarments or socks and shoes. The French mule operatives wear white cotton pants, undergarments, and a belt in place of a brace (Robertson). The American spinners wear woolen or linen shorts, depending upon the temperature in the mule-room, and shoes, but not socks (Heller).

Exposure to the lubricating oil is occasioned by oil sprayed off from the portion of the bare spindle immediately above the bearing, though for various reasons the amount of oil and the rate at which it is thrown off differ in various mills. A rough test with a piece of white, absorbent paper, hung from the bar for a definite period at different times after oiling, indicates that occasional drops may still be thrown off after two to three hours. It is from this source that the greatest amount of oil reaches the clothing of the workers, causing the trousers and lower parts of the shirt to be soaked with oil (Bridge and Henry; and Heller). It is not unusual to find oil in the lower parts of the trousers, originating from contact with carriage doors, or from spindle footsteps in machines without doors; and other parts of the pants are oily from kneeling or sitting down on the greasy floors, and from lying down during the cleaning job. Additional exposure to oil may be brought about by placing oily waste or the oil can in the pocket of the trousers, and rubbing oily fingers and hands dry upon the flanks of the overalls. Oily areas on the overalls are found, for these reasons, on both knees and on each thigh in front of the great trochanters extending around to the middle of the legs and groin in front. According to Owen's dust counter, there exist droplets of oil in suspension in the air of the mule room, the card room, and the ring spinning room, exposing to a minor degree the skin and clothing to oil.

Robertson has attempted to discredit the causal role of lubricating oil in the production of the so-called mule spinners' cancer, and has asserted that the cause is represented by mechanical friction in conjunction with the action of the blue aniline dye used in blue overalls. This claim has not found any recognition. It is an established fact that mule spinners' cancer was observed in Eng-

land long before the introduction of the blue overalls. The marked differences existing in the incidence of occupational cancers of this type in industries of other countries are attributable to the fact that they do not use shale oils, but less carcinogenic or noncarcinogenic petroleum oils, for the lubrication of the spindles. However, the type of lubricating mineral oil used in English textile mills has changed since its introduction. Henry reported that the early mineral oil employed in cotton mills in England was obtained from Parrot coal and Rorbanite mineral (1850 to 1862). Later, the oil was distilled from Scotch bituminous shale. Recently, oils have been imported from Pennsylvania, Rumania, California, and Mid-Continental oil fields. These were blended with domestic, shale oils to reduce the carcinogenic potency of the oils used.

Paraffins. A carcinogenic hazard from paraffin exists for men employed in those occupations, which entail a contact with crude or impure paraffin, i.e., a product which contains appreciable amounts of crude mineral oils. The main group of workers exposed to crude paraffins are men employed in the manufacture of this substance, and here, especially men working in the paraffin shed, and the sweating shed. The men employed in the filter presses work with bare hands and arms, although they wear canvas bibs and leg covers. They come in contact with oil containing scale, especially when they clean canvas filter bags by hand, which is an extremely greasy job. They get thoroughly smeared with the pressed distillate, and their clothes are soaked with oil (Ehrlich; Davis; Heller; Scott; Müller; Kennaway; and Wood). Such an exposure is accentuated if the workers are unclean. Ullmann, for instance, reported that Galician workers used to sleep in their soiled working clothes. In addition to these paraffin workers proper, who have a direct contact with paraffin containing crude oil, workers of other occupations are, also, exposed to this material (shale breakers, ammonia workers, and laborers) (Kennaway). A potential hazard exists for all those workers who handle incompletely purified paraffin (printing trade, and the manufacture of cartridges and explosives). So far, occupational contact with pure paraffin has never given rise to cutaneous malignancy, or any other trace of inconvenience (White).

IV. GEOGRAPHIC DISTRIBUTION AND INCIDENCE

The first description of an occupational paraffin cancer of the skin was rendered by von Volkmann in 1875. He observed three cases of this disease among workers employed in paraffin plants near Halle, Saxony, where paraffin is obtained by the distillation of lignite. Additional cases from the same source were recorded by Tillmanns in 1880 (1 case), Schuchardt in 1884 (1 case), and Eckardt in 1886 (4 cases). Liebe added another case in 1892 and mentioned a second new one, which was observed by Frey. In 1893 Tuteur noted an additional case originating in an employee of a German paraffin plant.

Almost 30 years passed before a new case of industrial paraffin epithelioma was placed on record in Germany. In 1924 Leitch mentioned that not a single

case of paraffin cancer had occurred in this country during the preceding 38 years. Kennaway attributed this fact to radical changes, which had been introduced in production methods, and to the institution of effective, preventive measures in German plants. Unfortunately, at the time when these claims were made by this English observer, there existed reports of new cases of paraffin cancer in Germany. Küntzel recorded, in 1920, a case from the industrial district of Saxony. Roesch followed in 1923 with a new case, while the most recent instance of paraffin epithelioma was published by Müller in 1932. The total number of paraffin cancers placed on record from Germany is, at present, 18 cases.

It is noteworthy that not a single case of occupational oil cancer has been reported from Germany. Although numerous dermatoses, from the use of various substitutes of lubricating oils, greases, and vaselines prepared from tar, were observed during the World War and during the years following it, it is unknown, whether any malignant sequelae were noted (Koelsch; Bettmann; Hoffmann; Riehl; and Blaschko). Buschke and Curth stated that investigations conducted by German workers' organizations had demonstrated that cutaneous malignancies did not occur among workers employed in textile mills, in contrast to the high incidence of such reactions among English mule spinners. These investigators suggested that the reason for this striking discrepancy was as follows: as German yarns were thicker than English ones, the spindles in German mills revolved at a slower rate than the spindles in English mills, and, therefore, were throwing the lubricating oil into the air to a lesser degree. Berg stated, however, that the real reason for the absence of mulespinners' cancer in Germany was the use of a lubricating oil different from that employed in English mills, where blends of shale oils were the offending agents.

The occurrence of paraffin cancer among workers employed in Galician oil refineries in the vicinity of Drohobicz was first reported by Ullmann (1912), who saw one case of carcinoma and one case of papilloma while making a survey of these establishments. This investigator was informed at that occasion that 12 additional cases of paraffin carcinoma had been observed there during the preceding 8 years. Müller noted in a report of 1932 that the incidence of paraffin cancer among workers in the Austrian-Galician oil fields during the period 1902 to 1912 was as follows: 10 cases in workers of 20 plants in Borysław; one case in Pressburg; 2 cases in Mährisch-Ostrau; and 2 cases in Jaroslaw. These industrial cancers have become less frequent during recent years, according to this investigator, a conclusion of significance, as Ullmann had stated in 1912 that these neoplasms were rarely met with in Austria and Galicia, whereas precancerous manifestations, such as diffuse and localized hyperkeratoses and warts, were frequent among workers of the Austrian-Galician oil industry. Ehrlich added in 1918 five new cases which he discovered

among 110 workers employed in a petroleum refinery in Moravia. Since only a small percentage of these 110 men were actually engaged in the manufacture of paraffin and had little appreciable contact with crude paraffin during the 20 years of operation of the plant, Ehrlich concluded that these neoplasms appeared in 50 to 60 per cent of the exposed workers at approximately the same time. Müller mentioned in his dissertation (1932) that Wilder had seen, within 8 to 10 years, twelve cases of paraffin cancer in the Galician district. The most recent case was reported in 1925 by Eiselsberg. As it is likely that the above-mentioned figures contain a certain amount of duplication, the number of paraffin cancers recorded from the Austrian-Galician region may be estimated to be about 25 cases. Oppenheim (1929) reported from Austria a case of oil cancer which he observed in a metal grinder.

Regarding the occurrence of proliferative, cutaneous manifestations among workers of the Rumanian and Russian oil industries, Ullmann had noted in 1912 that warty hyperkeratoses were frequently seen among Rumanian and Russian workers. Baader, on the other hand, emphasized the fact that not a single case of oil or paraffin cancer had been observed in Rumania; and Kolesnikow made a similar statement concerning the occurrence of malignant reactions in the employees of Russian plants near Grozny.

Paraffin and oil cancers are unknown in the Netherlands (among 342 of 400 workers employed in cotton mills examined) and Belgium [among 2,020 workers employed in 8 cotton spinning factories (Carozzi)]. Bainbridge, asserted, without giving any definite and detailed data concerning the source of his information, that many Belgians, who had been put to work as German prisoners during the World War in German paraffin factories, had contracted there paraffin epithelioma of the hands. Considering that the time of exposure to the carcinogenic agent for these cases would have been exceptionally short, that the location of the resulting tumors would be unusual, and that the recent statements of Belgian investigators, concerning the occurrence and incidence of occupational cancer in Belgian workers, make no mention of these cases, it appears more than probable that Bainbridge's claim rests on misinformation, particularly as similar observations have not been recorded concerning German workers, who doubtlessly were employed at the same time in the same operations. Buschke and Curth mentioned briefly that scrotal cancer caused by occupational contact with lubricating oils has not been seen among cotton spinners in Italy and Spain.

The first cases of oil cancer in France were reported by Derville and Guermonprez in 1890. They found one case of cancer and three cases of multiple papillomas among 300 to 400 workers employed in oil refineries located in the region of Roubaix, Loos, and Douai. These investigators were told at that time that similar manifestations were found among workers of the oil refineries of the Paris district. No further report has appeared concerning the

occurrence of neoplastic manifestations among workers employed in the French oil industry, in spite of the fact, that this industry has expanded greatly since 1890.

A case of occupational hyperkeratosis and melanosis in a lathe worker caused by contact with crude mineral oil was recorded by Sézary, Pasteur, Vallery-Radot, and Benoist in 1927. Two years later Pautrier and Diss found a similar condition in a worker employed in an automobile factory. The second case of oil cancer in France was observed by Lambret in 1932, who noted the occurrence of a scrotal cancer in a greaser employed in a weaving mill. A somewhat doubtful case of oil cancer of the hand was reported by Gougerot and Meyer in 1935. The development of the malignant growth was related to the injury of the hand soiled with lubricating oil by a bronze splinter. A similar combination of a cancerous growth following an accidental trauma to the back of the hand soiled with lubricating oil in a motor driver was reported by Moran. Carozzi stated in 1934 that an enquiry conducted among 14 spinning plants located in northern France near Lille-Roubaix had shown that oil cancer was almost non-existent there.

The first cases of paraffin cancer in Great Britain were described by Bell in 1876, who observed two cases of scrotal carcinoma in workers of Scottish paraffin plants. Three years later Cameron published an additional case. In 1883 Longmuir mentioned the occurrence of cutaneous malignancy among paraffin workers in England. Almost 25 years passed before Kirk added two new cases of paraffin cancers to this list. They affected men employed in paraffin refineries in which Scottish shale oil was fractionated. Kirk noted that the high incidence of epithelioma among workers employed in the shale oil industry in Scotland, particularly in paraffin plants, was a well-known fact among the local physicians.

During the decade following this report the general interest in these important, occupational cancers seems to have reached a vanishing point, because, when Ross published his treatise on industrial cancers in 1918, he merely noted the occurrence of warts on the arms of paraffin workers, and stated that these proliferative manifestations were found in 50 per cent of the press men. That paraffin cancer among Scottish, shale oil workers had not become extinguished during these years is indicated by a statement of Southam and Wilson, concerning the incidence of scrotal cancer in tar and paraffin workers (22 cases), observed at the Manchester Royal Infirmary during the years 1902 to 1922. Leitch mentioned in 1922 the occurrence of carcinomas and the absence of sarcomas among workers of paraffin refineries. Legge stated that 8 cases of paraffin epithelioma had been certified to the Factory Department during the years 1920 to 1922.

In the first comprehensive report on this occupational disease published by Scott in 1922, it is recorded that there were 19 cases of paraffin cancer during 1900 to 1921, which were observed among a total of 200 workers, em-

ployed in the crude paraffin departments of Scottish Oils, Ltd. Scott stated that these 19 cases represented a yearly incidence figure of 0.5 per cent. Two years later, Leitch quoted Scott to the effect that there had occurred, during the preceding 25 years, a total of 65 cases of paraffin cancer among workers employed in the shale oil industry of Scotland. In a treatise on anatomical distribution of occupational cancers prepared by Kennaway (1924), this investigator noted 19 cases of paraffin cancer in press men, referring apparently to cases included in the previously mentioned reports. In 1928 Scott reported again on this occupational neoplasm. He recorded that 89 cases of paraffin epitheliomata had been seen in workers of the Scottish shale oil industry during 1900 to 1928. Thirty of these cancers had affected men employed in the crude paraffin department, while an additional 59 cases were found in men of other grades of labor connected with the distillation and refining of shale oils. As approximately 5,000 men were employed by Scottish Oils, Ltd. annually, the cancer incidence per year was 0.1 per cent or 2 per cent for the 28 years surveyed. This figure is remarkably low, because a large number of workers have been included in this statistical analysis, who had either none or no appreciable and prolonged contact with crude paraffin or the oils expressed from them. These statistical data are for this reason, grossly misleading as to the actual incidence of paraffin cancer among the restricted group of workers who are exposed to these agents to any considerable degree.

Bridge and Henry reported in the same year and at the same occasion (International Cancer Conference, London, 1928) that 28 cases of paraffin cancer had been certified during 1920 to 1926 to the Factory Department. This figure was increased by two new cases during the following two years (1928) and 6 additional cases were recorded up to 1931, according to the Annual Reports of the Chief Inspector of Factories and Workshops for 1928 to 1931. The report in 1938 listed 9 new cases. The total number of paraffin carcinomas recorded in Great Britain since 1875 is about 150 cases. It cannot be maintained that this figure is near the actual number of cases which have occurred in this country, particularly before 1922.

However, the number of recorded and actual cases of occupational paraffin cancer is relatively small, when compared with the number of oil carcinomas which have been placed on record from Great Britain. The first studies of this industrial neoplasm were made in England by Wilson, who collected, in 1910, data about the occurrence of scrotal carcinoma in mule spinners of the Lancashire district caused by an occupational contact with lubricating oil (Brockbank and Stopford). Wilson observed, according to these investigators, from 1902 to 1910 at the Manchester Royal Infirmary 34 cases of scrotal cancer, of which 25 cases were present in mule spinners. Since a report of the Registrar-General from the year 1885 mentioned that there were from 6 to 7 deaths yearly from scrotal cancer among the inhabitants of South Lancashire, and in view of the relative rarity of the scrotum as a site of cutaneous malignancy,

it is probable that this industrial neoplasm was prevalent among mule spinners of this district long before the period covered by the investigations of Wilson. It was not until 1922 that the etiological relation between the exposure to lubricating oil and the genesis of scrotal cancer in mule spinners was actually established. Southam and Wilson, while analyzing 141 cases of scrotal cancer observed at the Manchester Royal Infirmary during the years 1902-1922, noted that in 69 cases of this series (53 per cent) the tumors affected mule spinners employed in local cotton mills. A subsequent survey made by Leitch on the incidence of mule-spinners' cancer showed that no less than 20 per cent of the fatal cases of cancer of the scrotum in England involved cotton spinners. There had been, according to unpublished data of the Registrar-General for England and Wales, during 1913-1914 ninety fatal cases of scrotal cancer of which 18 cases or 20 per cent affected mule spinners. During the years 1912 to 1922, 107 men had died from this disease, of whom 26 (24 per cent) were mule spinners. Fifteen fatal cases of scrotal cancer among mule spinners were noted in 1923. Leitch estimated from these data that there was in England and Wales a yearly average of 11.8 cases of fatal scrotal cancer in mule spinners, or one fatality in 2,000 spinners employed per year [calculated on the basis of 23,000 adult male mule spinners employed (female mule spinners are exceptional)].

As subsequent investigations showed that oil cancers in mule spinners affected other parts of the skin besides the scrotal sac, White was able to note in 1926 that there were 539 cases of occupational cutaneous malignancy among cotton spinners on record. When one year later Robertson reported on the causative factors active in the production of mule spinners' cancer, he cited a total of 469 cases of this industrial neoplasia, which had been observed from 1900 to 1925 by various agencies [Blackburn Royal Infirmary (1920 to 1925), 34 cases; Manchester Royal Infirmary (1902 to 1921), 69 cases; (1922 to 1924), 16 cases; Association of Operative Spinners (1917 to 1925), 173 cases; Cases of Scrotal Cancer of Spinners and Deaths Therefrom 1923 to 1925 Notified to Home Office, 125 cases]. The committee appointed in 1925 by the Secretary of State for the Home Department of Great Britain for the study of mule spinners' cancer found records of 539 cases of skin cancer among mule spinners for the years 1876 to 1925, with evidence of a rapid increase in incidence of this disease during the last years of the period surveyed. This last observation seems to be confirmed by a statement of Southam in 1928, when he noted that there occurred each year 50 new cases of scrotal cancer among mule spinners, and that the incidence of this industrial neoplasia was approximately 2.5 cases per 1,000 mule spinners per year. In the same year Bridge and Henry listed 418 cases of occupational mineral oil cancer, which had been notified to the Factory Department between 1923 and 1927. 361 of these cases occurred in mule spinners and 57 in employees of other industries. Skin cancers by mineral

oil products were seen, according to Bridge and Henry, in oilers and greasers employed among machinery, engine tenders, mechanics, and certain operatives of engineering trades. Since 1920 cancers due to mineral oils were reported in 17 cotton mill workers other than spinners, 11 engineering workers, 9 textile machinists, and 2 woolen mill workers.

Bridge and Henry commented that, apart from cancer caused by shale oil and spindle oil in mule spinning, the incidence of oil cancer in other industries was not high. These investigators believed that this was partly due to the lack of belief of the medical man, who should report them, that any cancer was occupational. Refining of foreign mineral oils in England had at that time, in the opinion of Bridge and Henry, not been carried out long enough to have resulted in the production of malignant skin lesions.

The Annual Report of the Chief Inspector of Factories and Workshops for the Year 1928 listed for the year 1928, 101 additional cases of mule spinners' cancer, and 4 cases of mineral oil cancer among members of other trades. The reports of this agency for 1929, 1931 and 1937 recorded the following data as to the incidence of mule spinners' cancer and oil cancer:

Years	1929	1930	1931	1932	1933	1934	1935	1936	1937	Total
Mule Spinners	54	82	60		63	41	62	61	39	462
Other Industries	20	15	18		6	5	5	7	7	83
Total										545

Henry found, according to the report for 1929, oil cancer in 2 workers and keratoses located on the forearms in 6 workers employed in the manufacture of oil gas (used for lighting railway carriages) from a mineral oil mainly composed of shale oil. An additional case involving the left hand was observed in a machine minder at a rope works, who came in contact with mineral lubricating oil used in a compound rope-making machine.

When Henry and Irvine published in 1936 their report dealing with the occupational distribution of scrotal cancer in the Blackburn Registration District where plants connected with the cotton trade (weaving, dyeing, bleaching, and finishing) are located, they made the following observations: The earliest report of a scrotal cancer in a spinner of this district was made in 1898; the incidence of this disease in the district increased steadily since 1910; with 1,502 mule spinners employed in Blackburn in the year 1921, there were 111 cases of scrotal cancer reported for this occupational group during the period 1837 to 1929, or 74.0 per 1,000 employed spinners in 1921. In an abstract of a thesis on the same subject, published in 1935, Irvine pointed out that the incidence of scrotal cancer and of cutaneous cancer of other sites was far in excess in mule spinners than that seen in other cotton operatives or other workers

in general. There were, according to Irvine's data, 133 cases of skin cancer treated in 1930 in a population of 1,502 cotton mule spinners (1921 census). Ninety-four of these tumors involved the scrotum and were typical mule-spinners' cancer. The rest of the neoplasms were situated in other parts of the skin. In the following year Henry analyzed the occupational records of 1,487 males with fatal scrotal cancer, which had been reported to the Registrar-General of England and Wales during 1911 to 1935; and prepared the following tabulation, arranged in quinquennial periods, concerning the incidence of this disease among mule spinners:

Years	1911–15	1916–20	1921–25	1926–30	1931–35	Total
Scrotal Cases	40	56	77	92	80	345
Other Sites of Skin	15	19	23	24	23	104

There were 449 cases of oil cancer officially recorded in England and Wales during a period of 25 years (1911 to 1935). Approximately 75 per cent of the cutaneous, industrial oil cancers were located on the scrotum. Henry attempted to obtain information concerning the approximate risk of mule spinners to contract oil cancer. He correlated the number of operatives employed in the cotton spinning industry with the number of cases of skin cancer observed during various periods (1911-1915: 42,000 workers and 8 cancers per year; 1921-1925: 28,000 workers and 15.4 cancers per year; 1931-1935: 33,000 workers and 16 cancers per year, making a crude death rate of 190,550 and 480 per million, respectively). Henry concluded that the figures obtained were by far too low, considering that the suggested figures of the population at risk were without doubt greater than the actual ones used for his calculation. Finally, reference may be made to a case of oil cancer in a gunsmith who used mineral oil (Rangoon oil, paraffin oil, and vaseline) in his work (O'Donovan). The total number of mineral oil cancers placed on record in Great Britain is well above 1,500 cases.

The following information, concerning the occurrence of oil cancer, is available from Asia. Koinuma noted in 1930 that up to the year 1928 no reports in regard to industrial oil and paraffin cancer were made in Japan. This observation was corroborated by Nagayo and Kinosita (1940) concerning oilers employed in Japanese cotton mills. Buschke and Curth stated that oil cancer was unknown among workers employed in the cotton mills of India. Relatively few workers remain in these operations for more than a few years. Thus, the observation does not exclude the possibility that the occurrence of delayed cancerous responses among former cotton spinners in India has escaped the attention of the investigators, from whom Buschke and Curth received their information. This suspicion is based on the fact that

during recent years skin cancers have been found in men engaged in spreading crude mineral oil over stagnant bodies of waters in the Indian tropics, as a means of combatting the mosquito plague.

The first cases of paraffin cancer in the United States were reported by Schamberg in 1910, who studied 18 cases of this disease observed in paraffin plants in Chicago, Ill. Four years later Davis published an additional case found in the paraffin department of an oil refinery of the same city. Upon inquiry at two paraffin plants, one located at Cleveland, Ohio, and the second at Franklin, Pennsylvania, Davis received the information that similar skin lesions had been observed among workers employed in these factories, but none of these manifestations had been of a malignant nature. In 1915, Hayhurst established the fact that paraffin cancer existed in handlers of crude heavy products in oil refineries of Ohio. When Wood visited, in 1929, fifteen oil refineries located in Pennsylvania, ten of which manufactured paraffin and employed a total of 1,500 men with 76 men handling this wax, he was told by the plant physicians and managers that not a single case of paraffin cancer had been observed among workers employed in these operations. The labor turnover in these plants was stated to have been low, and the majority of workers had been employed for 5 to 41 years. Wood concluded on the basis of these data that pure paraffin as well as Pennsylvania mineral oils were not productive of cancer.

While the reports of Schamberg, Davis, and Hayhurst had shown that this contention was not applicable to American oils in general, this observation was emphasized by reports concerning the occurrence of paraffin and oil cancers in American refineries published during the following years. Wise recorded the occurrence of a skin cancer in a paraffin worker, who had a typical paraffin keratosis, and noted that some of the men employed in the same branch of the factory were suffering from similar skin lesions. Heller found two cases of paraffin cancer in press men employed in a refinery located in the Middle West, in which Midcontinental oils having a mixed base were processed. Eight additional cases were reported, according to Heller, from a refinery employing 400 men and using crude oils from Indiana, Illinois, and Ohio. Five cases of paraffin cancer were notified to the Industrial Hygiene Division of the Ohio State Department of Health from 1928-1929. These neoplasms were seen in men engaged in plants using oils from the Lima fields (Ohio). Heller mentioned, moreover, three cases of paraffin cancer, which occurred from 1926 to 1928, among workers of a paraffin department employing on the average 30 men. Twelve additional cases of oil and paraffin cancer were collected by Heller from the records of the Memorial Hospital, New York, and the New York Skin and Cancer hospital. This made a total of 20 cases of paraffin and oil cancer observed in the United States, according to this investigator.

Haagensen made in the following year an analysis of the occupational

cancers cared for at the Memorial Hospital from 1917 to 1930, and found a total of 11 cases of oil and paraffin cancer, involving seven men employed in oil refineries and four men engaged in occupations entailing contact with lubricating oils. Haagensen contended that two cases of this series were not of occupational origin, as the tumors were located in the face and lip, respectively. This claim cannot be recognized any longer as correct, as Heller observed 21 cases of epithelioma of the face and lip in men working in petroleum refineries; and English experiences recorded in this respect leave no doubt that oil and paraffin cancer may affect the face and the lip. Mention may be made, finally, of a statement of von Eiselsberg (1925), which has been quoted in the literature [Bering and Zitzke (1935)] and for which a factual basis could not be ascertained. This investigator contended that in a series of 141 scrotal cancers reported from the United States and observed during 1905 to 1925, 23 cases occurred in paraffin workers and 69 cases in silk spinners.

In addition to the four oil cancers mentioned by Haagensen, there exist only a few reports mentioning the occurrence of this type of industrial neoplasia in the United States. When Hoffman investigated, in 1928, the problem of oil cancer (mule spinners' cancer) in the United States, he noted that among 6 scrotal cancers found in textile workers 3 were present in mule spinners. But one of them came from Canada and two had immigrated from England. Of the other three textile workers, two had been born in England and one, a carpet worker, had worked there. Hoffman expressed, on the basis of this evidence, the suspicion that in all six instances an occupational contact with carcinogenic lubricating oils had taken place outside of the United States. Subsequent studies of Heller covering the same subject have shown that mule spinners' cancers have been contracted definitely in this country. Heller's inquiries at 14 cotton mills located in New England (mainly New Bedford), where the machinery and practice of spinning is similar to that used in England, and where between 500 to 1,000 spinners were employed (1926 to 1929) were negative. He did find at the Massachusetts General Hospital in Boston records of 25 fatal scrotal cancers, which had been observed there between 1887 and 1928, and of which six involved mule spinners. Heller proved that two of these cases originated in the United States. None of these cases occurred during the last fifteen years. Apart from a change in the spinning technique, which was developed in more recent times and which brought about a gradual replacement of mule spinning by the less hazardous ring spinning, Heller expressed the opinion that the character of the lubricating oil used in American plants accounts for the great rarity of mule spinners' cancer in the United States. Heller pointed out that American spindle oils are harmless in carcinogenic respects because this type of lubricating oil is more intensely treated with sulfuric acid than the ordinary lubricating oils.

This insures the removal of impurities and unsaturated hydrocarbons, and produces an oil suitable for high speed machinery and non-oxidizing in a highly humid atmosphere.

The occurrence of oil cancer in other professional branches seems to be equally rare in the United States, if the available data give a reliable picture of the actual situation. Leonardo recorded in 1938 the presence of an oil cancer in a lens grinder who used an oil consisting of equal parts of kerosene and shale oil. In an analysis of 62 cases of cancer of the eyelids Sharp mentioned, that occupational contact with refined lubricating oils played an etiological role in the production of these tumors.

The total number of paraffin and oil cancers recorded in the United States so far is comparatively small, comprising approximately 50 paraffin carcinomas and a dozen oil cancers.

In commenting on the apparent rarity of paraffin and oil cancer in view of the immense extent of the oil industry, Kennaway (1925) suggested the following possible causes for this phenomenon: 1. In many countries medical inspection of industrial workers and publication of records on industrial diseases is not well organized. 2. The industrial growth of the petroleum industry is of rather recent date; consequently, an insufficient amount of time has elapsed for a development of oil cancers on a large scale. 3. In some countries, such as the United States, the number of native workers employed in oil is not very large. The unpleasant work is left to newcomers. 4. Many kinds of petroleum do not produce cancer. 5. Some petroleums (Californian) do not produce cancer when in the original state, but only after being heated during the distillation process, which forms aromatic compounds with carcinogenic qualities not present in the crude oil. These suggestions need only minor modifications to make them applicable to present times and existing conditions.

Brief mention may be made of the effects which have followed, in some instances, the medicinal use of paraffin and mineral oil. The subcutaneous injection of soft and hard paraffin for cosmetic purposes (cheeks, nose, ears, breast, and penis) has resulted in a number of instances in the development of chronic, foreign body granulomas, known as "paraffinomas." Ullman contended that such untoward tissue reactions are produced by the use of an impure paraffin and vaseline, as paraffinomas appear in only a small percentage of individuals subjected to this type of therapy (Fischer and Birt; Tanfiljew; Jaerisch; Hueper; Eitner; Masson; Körbler; Rose; Krohn; Cruickshank; Davis; and Schmorl). There are two cases on record in which the introduction of paraffin into the female breasts was followed, after a long latency period, by a mammary cancer (Schmorl; and Rose). The evidence connecting the two events is not conclusive. The malignant growth in Schmorl's case appeared many years after the intramammary injection of paraffin at the site of the previously amputated breasts, which at the time of the operation were

entirely unsuspected of malignancy. In the case reported by Rose the carcinoma developed in and around the mammary tissue, infiltrated with paraffin 20 years previously.

Experiences in the industrial field (White), and to a much greater extent, in the medicinal and cosmetic field attest the fact that paraffin, vaseline, and paraffin oil are noncarcinogenic provided they are freed from impurities. The medicinal evidence must be considered especially convincing since these substances form the base of skin creams and ointments placed on a diseased skin and open ulcers, in this way furnishing favorable conditions for neoplastic responses in case such agents contained carcinogenic components.

V. SYMPTOMATOLOGY

While Ogston was the first to describe the clinical symptoms of paraffin dermatosis (1871), it was Volkmann who recognized that these cutaneous lesions, which were first of acute nature and later assumed a chronic character, lead to the development of epitheliomas. Subsequent investigators, particularly Tillmanns; Ullmann; and Scott have confirmed, elaborated, and systematized these earlier observations.

The acute manifestations of oil or paraffin skin, which develop during the first months of occupational contact with crude paraffin and semi-refined oil, and which affect the majority of new workers, involve most frequently and extensively the hands, forearms, and regions of the scrotum and groin, that is, the regions having the most intense and prolonged contact with the oily material. Less often these lesions are found in the skin of the face, neck, thigh, legs, feet, abdomen, and between the shoulder blades. The initial symptoms consist of an erythema, appearing in the form of dull red patches irregularly distributed over the forearms and gradually merging with each other. The patches are slightly raised above the surface of the skin and are indurated. This erythematous stage may persist for a prolonged period and then, either slowly disappear or be replaced by chronic changes (sclerodermia, dryness, scaling, thickening, and brownish pigmentation [shagreen skin]). Sometimes, the patches have a psoriatic-like character; at other times they are acne-like spots and papules.

The papules are rice-seed to navy-bean sized cutaneous superficial, elevated indurations with a shiny surface and round shape. They do not contain any fluid, but a small amount of serous exudate may moisten their slightly depressed tips. They are painful upon pressure and itch when exposed to sunlight. It is characteristic of these papulous lesions that they are not surrounded by an inflammatory areola and they do not show any tendency to coalesce, even if it seems so when they are densely placed, such as found on the ulnar aspects of the forearm. A tiny, thread-like core, corresponding to a necrosed, sebaceous duct, may be expressed from the orifice located at the floor of the central depression, which may be occupied at other times by a hair (Scott).

They never affect the palms of the hands and the soles of feet. Upon cessation of exposure to irritating oils or often spontaneously, when a sort of tolerance develops, these papules pale within a few days, dry out, and disappear, leaving scaly and crusty lesions of psoriatic character, white, cicatricial spots, or brown pigmented foci.

In addition to these papulous efflorescences, there develop a varying number of comedones, resulting from the mechanical obstruction of the sebaceous ducts by oil, paraffin, and dirt. They are found mainly on the extensor sides of the arms and legs. As secondary infections in these obstructed glands are common, folliculitis and furunculosis ("wax-boils") are frequent occurrences. A pustulous dermatitis is rarely seen (Scott; and Ullmann).

While the majority of oil and paraffin workers seems to become immune to the injurious influences of crude and semi-refined minerals, some of them exhibit a progressive course. With continued contact to these agents the skin becomes dry, scaly, parchment or leathery-like, and covered with enlarged pores. The skin color assumes a dirty grey hue with dark brown spotting, and occasionally, with leucodermic areas (Eckardt). While a spotty melanosis usually accompanies the development of the chronic changes, pigmentary disturbances may be absent in the seborrhoeic skin (O'Donovan). Telangiectases are rarely seen (Wise; and Müller). Some of the papules develop, during the chronic stage, into hyperkeratotic thickenings, which appear in the form of small, pointed, pinhead-sized horns, larger, circumscribed, pea-sized, flat, greyish white, crusty or waxy elevations, rugose, yellowish-brown, thickened patches, or diffuse, ichthyosis-like thickenings of the skin. Some papules grow into warty structures of hard consistency and great permanency, unless a central necrosis develops, which causes a regression of the wart and the formation of a white scar at its former site. This chronic, hyperplastic stage of oil skin may persist for many years or for the rest of the life of these workers. It has been likened in its general appearance with the precancerous stage present in chronic radiodermatitis or xeroderma pigmentosum (Müller; and Wise). It can be distinguished from these conditions by the more extensive development of hyperkeratoses, in addition to the difference in the location of the lesions.

Neoplastic and malignant developments may start in such a skin from various sources. Some of the epitheliomata originate directly from papulous and verrucous lesions which are transformed into ulcerative or cauliflower-like, cancerous manifestations. Scott rendered the following description of the changes accompanying the cancerization of a papulous lesion: A central necrosis may be combined with a gradual growth of the lesion, ultimately resulting in an ulcer with surrounding elevated and indurated edges. The indurated edges become undermined. The ulcer surface is covered by red, easily bleeding granulations. The epithelial tissue in the edges forms cauliflower-like excrescences.

The malignant transformation of scaly warts presents, according to Scott, the following picture: If the scales are removed from a benign wart, an indurated base is left not protruding, to any extent, above the general level of the skin. When proliferation occurs, it becomes raised above this surface up to one-half inch and extends in diameter, while a thick, horny layer of scales covers its surface. A tendency to form fissures appears or abrasions develop, followed by serous exudation and crusting. This condition persists for months, the area gradually increasing until the covering of warty growths sloughs, leaving an ulcer. The subsequent growth of this now malignant ulcer is slow. Malignant developments follow or set off in warts, when they are nipped in occupational accidents (Brockbank and Stopford).

Koelsch contended that malignant growths in oil skin do not always start from warts or papules, but may arise from necroses of the skin caused by local nutritive disturbances. Tumors of this origin are said to be relatively benign. Kennaway, on the contrary, asserted that the majority of paraffin and oil cancers does not arise from previously existing benign warts, but from independently formed reddish, pea-shaped nodules in which typical "cell-nests" are present from the onset, or, in the scrotum, from simple, ordinary, papillomatous warts, moles, or small cysts normally found in the skin of this organ. While it may be conceivable that such a nonoccupational, cutaneous abnormality may furnish the primary, precancerous lesion upon the basis of which a specific oil or paraffin cancer develops, it must be doubted seriously that this is a common occurrence. Southam and Wilson as well as Küntzel contended that the hyperplastic lesions, from which cancers are formed, are malignant from the start and unrelated to the ordinary, papillomatous warts found. According to the statements made by Southam and Wilson, such primary malignant warts remain in the warty stage only for 4 to 6 months, and then become malignant growths.

VI. SITES AND LOCAL DISTRIBUTION

The site and local distribution of paraffin and oil cancers depend to a great extent upon the type of contact present in the various operations in which these substances are handled. Differences in the occupational composition of different series of paraffin and oil cancers, contained in the literature may account for variations in the local distribution of these neoplasms, listed by these sources.

Müller noted the various sites of paraffin cancer in the following order, arranged according to their relative frequency: 1. scrotum; 2. prepuce; 3. penis; 4. forearm; 5. upper arm. Scott, on the other hand, gave the following local distribution of a series of 30 paraffin cancers: 19 cases (63 per cent), arms, forearms, and hands; 3 cases (10 per cent), face, neck and ears; 5 cases (17 per cent), scrotum; 3 cases (10 per cent), groin.

The significance of the occupational factor as the cause of such discrepancies

is demonstrated by an observation of Kennaway. He stated that paraffin press men were most liable to develop cancer of the arms and hands, while many scrotal cancers were found among men in oil and paraffin plants belonging to other and very diverse occupations, many of which had no intimate or prolonged contact with oil or handled it or any of the substances present during the stages from the crude oil to the refined and ultimate product.

Heller stated that the incidence of scrotal cancer in men employed in the extraction of paraffin was four times higher than that in tar workers. The following table presents the local distribution of 105 cases of paraffin carcinomas collected from various sources without regard to the particular occupational activity of the individual cases.

LOCAL DISTRIBUTION OF PARAFFIN CANCERS

Organ	Head and Neck	Upper Limb	Lower Limb	Penis	Scrotum	Total
Cases	8	49	3	6	39	105

These data confirm, in general, the observations of Scott, and reflect the sites of the most marked and prolonged exposure to crude paraffin. The local distribution of the malignant paraffin lesions exhibits a certain degree of parallelism with that observed in dermatitis papularis, one of the precursor conditions found among paraffin workers, which shows the following distribution: arms and hands, 75 per cent; both arms and legs, 20 per cent; legs only, 5 per cent.

Concerning the local distribution of oil cancers, Haagensen remarked that 70 per cent were found involving the scrotum; while Southam mentioned, in connection with the mule spinners' cancer, that 75 per cent of these neoplasms affected the scrotal sac, especially its left aspect (left anterior aspect, 84 per cent; right side, 10 per cent; and midline, 6 per cent), and the remaining 25 per cent of oil tumors were distributed upon the forearms, neck, and face. The skin of the legs exhibits a remarkable and peculiar degree of resistance as oil cancer is rarely found on the lower limb. Scott presented the following compilation on the local distribution of oil cancer: scrotum, 34 cases (58 per cent); arms, forearms, hands, 14 cases (23 per cent); face, neck, ears, 9 cases (15 per cent); legs, 1 case (2 per cent); anus, 1 case (2 per cent). The following table presents data on the local distribution of 691 cases of oil cancer, which are divided into two groups; one series of 418 cases of mineral oil cancer composed of cancers in mule spinners and other operatives in contact with mineral oil (compiled by Bridge and Henry), and the second series are of 330 cases of oil cancer (collected from various sources).

LOCAL DISTRIBUTION OF MINERAL OIL CANCERS

Site	Bridge and Henry			Collected Series	Total
	General	Mule-Spinners	Others		
Head and Neck (forehead, temple, nose, cheek, ear, lip, eyelid)	31	25	6	140	171
Upper Limb	44	38	6	30	74
Lower Limb	17	15	2	5	22
Scrotum	303	268	35	150	453
Other Sites (Anus, Penis)	23	15	8	5 (Anus 1, Penis 4)	28
Total	418	361	57	330	748

While both statistics demonstrate the high incidence of scrotal cancers in oil workers, there is a much greater proportion of cancers of the head and neck in the series collected from numerous sources than in that recorded by Bridge and Henry. The reason for this discrepancy is probably referable to the fact that the collected series contains cases from highly diverse occupations, entailing a more intense exposure of the head and neck; while the data contained in the analysis of Bridge and Henry are drawn mainly from a few definite occupations, having a more specific and restricted type of contact. The low incidence of oil cancer of the lower limb among mule spinners deserves special mention, as these operatives work with bare feet on an oily floor and wash these parts of their body not more than once a week. As not a single instance of oil cancer of the sole and only one case of cancer of the anterior surface of the ankle has been recorded, this apparent immunity may be explained by the assumption that the work with bare feet hardens the skin and makes it little permeable to the oil.

A great deal of thought and speculation has been expended to advance plausible reasons for the frequent involvement of the scrotum by cancer in paraffin and oil workers, particularly in mule spinners. The existing evidence suggests that the skin of the scrotal sac must possess a special susceptibility to react with epitheliomatous growth upon contact with certain agents, such as unrefined oils, crude paraffin, soot, pitch, tar, and arsenic. However, it becomes equally clear from an analysis of the conditions of exposure present in those groups of workers, who are preferably affected by occupational scrotal cancer, that this scrotal affinity is not entirely an organ conditioned one, but depends to a marked degree upon the type of contact with the particular

carcinogenic agent, i.e., upon a direct exposure of the scrotal skin to the carcinogenic oil, in the instance of the paraffin and oil workers. The peculiarities of the anatomical structure of the scrotal skin offers under such circumstances favorable conditions for the retention and penetration of the carcinogenic agent. The rugosity of the skin favors the deposition of the oil in these folds, and permits an intimate and prolonged contact with these substances, which is accentuated by the fact, that this part of the body is not readily cleaned and frequently neglected in this respect. The presence of large pores and numerous sebaceous glands, the tendency to maceration of the skin under the influence of excessive perspiration, and the friction exerted by the clothes are factors which facilitate the penetration of the oily matter with its carcinogenic agent into the skin and accentuate its action. It has been maintained that contractions and relaxations of the dartos muscle in the scrotal wall may exert a suction upon the material deposited upon the skin, and favor an aspiration of this material into the sebaceous ducts.

Kennaway, who is not convinced that the rugosity of the scrotal skin accounts for the high incidence of scrotal cancer in mule spinners, and who pointed out that other parts of the skin, such as the umbilicus, toes, scalp, interscapular region, and back of neck, can store dirt as easily as the skin of the scrotum, contended that those oil workers develop scrotal malignancies, who are, also, exposed to ash, coke dust, or other gritty material, i.e., to conditions, which enhance the friction in the scrotal region. Kennaway argued that the relative rarity of cancer in the parts of the skin adjacent to the scrotum which have as close a contact with the carcinogenic agent as the scrotum but remain free from cancer support his viewpoint. While it may be possible that the skin of the penis and the scrotum may be soiled with oil by the workers during urination (Ullmann), this exposure is only a minor one compared with the direct and intense contact of the penis with oil contained in the oil-soaked parts of the trousers (Kennaway; and Küntzel). The relative rarity of cancer of the penis in oil workers (Leitch), existing under such circumstances of exposure, suggests that the anatomical structure of the penile skin plays a decisive role in this respect, especially as it differs markedly from that of the adjacent scrotal sac.

VII. MULTIPLICITY OF OIL AND PARAFFIN CANCERS

The diffuse contact of larger portions of the skin with carcinogenic oils and paraffins favors a multicentric development of the resulting neoplastic responses, which make their appearance either simultaneously or successively (Scott; Müller; Henry and Irvine; O'Donovan; Irvine; Roesch; and Ehrlich). Henry and Irvine noted a neoplastic multiplicity in mule spinners' cancer in 16 out of a total of 111 cases. In eleven of these cases a primary scrotal cancer was followed in five instances by a second scrotal neoplasm

within 3.75 to 21 years, in 2 instances, by a facial cancer appearing 8 to 16 years later; in one case, by a cancer located on the lower limb 3.25 years later; in two instances, by two tumors involving both the scrotum and the face or the face and the ear, respectively; and in one instance, by three subsequent neoplasms affecting the ear, face and nasal septum. The site of the primary cancer was, in other cases, the face or forearm, respectively, while the subsequent primary tumors involved the scrotum. Cases of multiple paraffin cancers were reported by O'Donovan; Scott; Volkmann; Ehrlich; Küntzel; and Müller. Scott observed up to four successive cancers in one paraffin-worker. O'Donovan's case had fifteen blastomatous lesions located on the nose, forearm, and ears. The primary cancer in the paraffin worker recorded by Müller involved the forearm, while the second neoplasm was situated in the scrotal skin. Multiple scrotal malignancies in paraffin workers were observed by Volkmann; Küntzel; and Ehrlich.

In addition to these instances of multiple cutaneous neoplasia, in oil-and paraffin workers, there are several cases of hetero-organic multiplicity of oil- and paraffin cancers on record (Southam; and Roesch). Southam mentioned that he observed in several mule spinners cutaneous scrotal malignancy in co-existence with primary cancers of the lung, tonsil, and stomach, that is, in organs which have a direct contact with the carcinogenic agent responsible for the cutaneous neoplasia, as the oil droplets sprayed into the air from the spindles are inhaled and swallowed, and reach the lung and the stomach. Roesch found in a paraffin worker three simultaneously existing, primary carcinomas affecting the scrotum, the lung, and the stomach.

VIII. COURSE AND PROGNOSIS

The oil and paraffin cancers do not produce readily metastases in the regionary lymph nodes. The scrotal neoplasms may invade the contents of the scrotal sac, and may extend to the base and shaft of the penis. Unilateral scrotal carcinomas may ultimately develop metastases in the lymph nodes of both inguinal regions, as the lymphatics of both sides of the scrotal sac form numerous anastomoses (Morley). Southam and Wilson observed that the primary malignant wart of the scrotum may heal, while the secondary deposits in the inguinal lymph nodes persist; a fact which has given rise to the incorrect diagnosis of primary cancer of the groin [(Irvine) (Similar observations were reported in connection with the chimney sweeps' cancer of the scrotum by Butlin)]. There is little tendency of the scrotal cancers to form distant metastases, while the involvement of the pelvic nodes, as a late development, is not uncommon. Recurrences in inguinal glands after the surgical removal of the primary tumor of the scrotum are not infrequent. Scott contended that metastases from oil cancers of the arms and hands into the regionary lymph nodes occur even later than those of scrotal malignancies. A fatal outcome is,

according to this investigator, more often caused by the effects of complicating infections and exhaustion than by metastases.

The prognosis is good for early cases of oil and paraffin cancers, and is for locally advanced tumors relatively favorable, as neoplasms of this type can be successfully treated with local excision without being followed in many instances by the appearance of recurrences or regionary metastatic growths (Southam; and Scott).

In the presence of glandular involvement, the outlook is considerably worse and recurrences are liable to occur after treatment of the primary lesions. The ultimate prognosis is aggravated by the fact that second primary tumors may develop after the successful eradication of the first cancer, and that such neoplastic developments may take place many years after the cessation of exposure to the injurious agents (Küntzel). The prognosis of oil and paraffin cancers of the skin follows the general rules, that is, it depends upon the stage at which the tumor is properly diagnosed and adequate treatment instituted.

The final outcome of many of the cases recorded was aggravated by the fact that the workers came under medical care at a late stage of the disease. Ignorance, negligence, and bashfulness, in addition to poverty, contributed to this attitude assumed by many workers, especially when the cancer involved the scrotum. It is, therefore, not surprising that the mortality from oil and paraffin cancer among the cases placed on record is relatively high, particularly during those periods in which medical supervision of the oil- and paraffin workers was either entirely absent or very deficient. Eckardt stated in 1886 that death was caused by recurrences or metastases in five out of eleven paraffin cancers observed, two additional cases were considered cured, while of four other cases the ultimate fate was unknown. During relatively recent years, a high mortality from oil cancer has been reported to be prevalent among the members of especially exposed groups of workers. Irvine mentioned that the comparative mortality figure for skin cancer from 1920 to 1923 in cotton spinners was 16 times higher than that of the general occupied and retired male population in England.

The following additional data on this subject were culled from various English sources: From 1920 to 1931 and 1933 to 1937, there were 45 notified cases of paraffin epithelioma of which 6 were fatal; during the same periods there were recorded with the Inspector of Factories and Workshops 924 cases of mule spinners' cancer of which 298 ended in death; while of 144 oil cancers among workers of other industries, 78 cases had a lethal outcome. In a treatise by Henry, dealing with fatal cases of occupational scrotal cancer, this investigator stated that there were, from 1911 to 1935, 877 notified cases of mule spinners' cancer, of which 449 were fatal (345 of these tumors involved the scrotum). Part of the cases of this series, while living at the time

of the statistical analysis, undoubtedly succumbed later to their occupational neoplasia. The prognosis of industrial oil cancer, as reflected by the statistical figures from England, is far from favorable and comparable to that found in cutaneous malignancy in general. Considering the rather benign, biological behaviour of these tumors and their relatively good response to properly and timely instituted treatment, the impression remains that a great deal more can be done to improve the prognosis of this industrial neoplasia (Twort).

IX. SEX

The great majority of the occupational paraffin and oil cancers is found among male workers. Bridge and Henry commented on the absence of oil cancer among female workers employed in spinning establishments in England (a total of 1,879 employed). They attributed this phenomenon to the facts that there were only a small number of female mule spinners and only a few of these remained in the trade sufficiently long to be adequately exposed; while others had left the industry before their industrial tumors became manifest. The occupational etiology of the subsequently appearing lesions was not properly recognized for this reason (475 of the 1,879 women employed in the spinning industry were over 30 years old and only 159 were over 40 years old). The majority of these women were working as piecers and scavengers, and not as mule spinners.

Southam (1928) expressed his astonishment regarding the uncommon occurrence of cutaneous cancer in female cotton operatives and mentioned the observation of an epithelioma of the forearm in a female cardroom worker. However, in 1930, Henry noted that recent notifications had been received concerning the occurrence of oil cancer among female weavers and cotton ring-spinning operatives. This information is in agreement with observations reported by Somerford concerning the occurrence of oil cancer of the skin in women who were or had been exposed during their work to mineral oils. In a series of 45 cases of cutaneous malignancy in women analyzed by this investigator, three individuals had, at the time of the discovery of the neoplasm, occupational contact with mineral oil, while an additional sixteen women had been exposed to oils in the past before their marriage. Somerford emphasized the fact that the only irritant of carcinogenic nature to which women become exposed during industrial work in England is mineral oil, as there were no cases of tar, pitch, or paraffin cancer in women in his series. In view of the decline of mule spinning in England since 1900 and the increasing use of ring- or flyer-spinning for which women are employed (Leitch; and Irvine), there may result in the coming years a gradual reduction in the number of mule spinners' cancer in male workers, and at the same time a higher incidence of oil cancer among industrially employed women may occur. It is not likely that such an increased exposure to mineral oils by women

employed in the textile industry will cause an excessive incidence of malignancy of the external female genital organs, because of the prevailing working conditions and the type of clothing worn by women. This conception is supported by a statement of Robertson, who mentioned that none of the female mule spinners employed during the World War were known to have developed cancer of the vulva. As carcinoma of this organ is not only rather rare, but also runs a highly malignant course in contrast to the slowly growing and spreading scrotal cancer, any unusual frequency of these neoplasms would have attracted attention readily.

X. AGE

The age distribution of paraffin carcinomas of the skin, as appearing from an analysis of 106 cases recorded in the literature (including those of Scott), is presented in the following table:

AGE DISTRIBUTION OF PARAFFIN CARCINOMA

Years	31–40	41–50	51–60	61–70	71–80	Total
Cases	6	30	38	29	3	106

The age range is thus from 31 to 80 years, while the peak of frequency is located during the sixth decade of life.

Cutaneous cancers caused by mineral oils exhibit a similar age distribution, presented in the following table, which does not include any instances of mule spinners' cancer.

AGE DISTRIBUTION OF MINERAL OIL CANCER

Year	31–40	41–50	51–60	61–70	71–80	Total
Cases	12	22	23	6	5	68

Although a corresponding statistical compilation as to age distribution of mule spinners' cancer is not available, Henry has furnished a detailed analysis of the number of deaths from scrotal and extra-scrotal, cutaneous cancer in mule spinners arranged in decennial groups and comprising 449 cases. Brockbank and Stopford mentioned that the average age of mule spinners' cancer is 51 to 52 years; while Southam noted that mule spinners' cancer involved men over 50 years old, and rarely occurred at an earlier age period, the youngest case of his series being 32 years old. The following table prepared by Henry presents the number of deaths in decennial groups from mule spinners' cancer.

NUMBER OF DEATHS IN DECENNIAL GROUPS FROM MULE SPINNERS' CANCER (Henry)

Site Years	25–34	35–44	45–54	55–64	65–74	75–84	85–	Total
Scrotal	1	20	87	131	83	22	1	345
Percentage	25	80	87	81.9	66.4	64.7	100	76.8
Non-scrotal	3	5	13	29	42	12	—	104
Percentage	75	20	13	18.1	33.6	35.3	—	23.2
Total	4	25	100	160	125	34	1	449

Henry could show by an analysis of the age at death from cutaneous cancer of mule spinners during the successive quinquennial periods of the 25 years (1911-1935), that the average age at death increased up to 12 years from 1911-15 to 1930-35. The following two tables were furnished by Henry in support of his observation:

AGE AT DEATH FROM SCROTAL CANCER IN MULE SPINNERS

Years	No. of Deaths	Average	30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85–
1911–15	40	54.2	1	3	2	2	11	12	6		3			
1916–20	56	65.2		1	3	6	11	18	9	5	3			
1921–25	77	58.3		2	3	10	14	12	17	7	9	3		
1926–30	92	60.8		1	2	7	14	19	13	20	10	6		
1931–35	80	63.5		1	2	6	6	15	10	12	14	13		1
Total	345	59.4	1	8	12	31	56	76	55	44	39	22		1

AGE AT DEATH FROM CUTANEOUS NON-SCROTAL CANCER IN MULE SPINNERS

Years	No. of Deaths	Average	25–	30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85–
1911–15	15	54.6	1			2	2	2	3	1	3	1			
1916–20	19	58.6		1			2	2	5	4		4	1		
1921–25	23	62.0			1		1	3	4	4	6	3		1	
1926–30	24	67.0			1	1			2	1	9	4	5	1	
1931–35	23	66.7		1				1	2	3	6	6	2	2	
Total	104	62.0	1	2	2	3	5	8	16	13	24	18	8	4	

The interpretation of this observation must be postponed until additional data are available. It cannot be concluded from this evidence that the potency of the carcinogenic hazard has been reduced and has caused a considerable lengthening of the exposure time. It is just as possible that the age at which the workers enter the hazardous operations has been advanced during recent

years, and, for this reason, the manifestation period and average age at death has been shifted into an older age period. The conditions existing in this respect in connection with the similarly located, chimney sweeps' cancer of England seem to support this concepton. The average age of men affected by scrotal soot cancer has increased greatly, since the law forbids employment of boys as apprentices in the chimney sweeps' trade. Somerford remarked, concerning the age at which the occupational activities were started in England, that "it was an almost routine practice for children, both male and female, to work in the mill on leaving school, and in many cases as half-timers from the age of nine or ten."

The presented data indicate that the average age of workers, affected by paraffin- or oil cancer during recent years, does not differ appreciably from the average age at which other accessible and cutaneous, malignant tumors of unknown etiology make their appearance [lip cancer: average age, 59.8 years; penile cancer: 52.1 years; and scrotal cancer: 51.9 years (Brockbank and Stopford)]. This suggests that the carcinogenic factors operative in the production of these so-called "spontaneous" cancers are of similar potency, and exert their preparatory influence over a period corresponding to those present in the development of occupational oil- and paraffin carcinoma.

XI. EXPOSURE TIME

The time of exposure necessary for eliciting a cancerous response in the skin of individuals occupationally exposed to crude paraffin and semi-refined and refined oils and greases varies widely. The minimum time required is ten years, but exceptions of shorter exposure seldom occur.

The exposure time for paraffin carcinoma is from twelve to thirty years (usually more than 20 years), according to Scott. The following compilation represents the exposure times recorded for 58 cases of paraffin cancer.

EXPOSURE TIME OF PARAFFIN CARCINOMA

Years	1–5	6–10	11–15	16–20	21–25	26–30	31–35	Total
Cases	2	2	17	12	8	9	8	58

These figures demonstrate rather conclusively that the average exposure time to paraffin carcinoma is shorter than that observed by Scott, who is supported by Ehrlich. They are in agreement with the data supplied on this matter by Oliver; Tillmanns; Zweig; and Eckardt, who noted that the average contact period was ten years or more. Paraffin cancer may become manifest many years after the cessation of an occupational exposure to crude paraffin. Roesch reported a case in which the neoplasm appeared 33 years after the start of the exposure and 21 years following the discontinuation of the hazardous work.

The occupational carcinogenesis of the skin caused by mineral oil requires a prolonged period of exposure. Southam placed the minimum exposure time of shale oil cancer at rarely less than 10 years, at which time the precancerous warts make their appearance. Henry (1929), who analyzed large series of cases of mule spinners' cancer for this point, mentioned that the shortest period of exposure observed was 16 years and the longest 63 years; while the maximum incidence occurred after 39 years of contact with the shale oil lubricant. Henry presented his observations on this subject in the following table:

EXPOSURE TIME OF MULE SPINNERS' CANCER (Henry)

Exposure Time Years	15–19	35–39	40–44	45–49	50–54	55–59	60–64
Percentage of Cases	0.6	18.6	18	15	15.6	8.3	3.0

Henry noted that the cancers appeared at a later date than usual, when the exposure either ceased before a neoplasm had appeared or was interrupted for some time.

In the following table the distribution of cases upon the various exposure periods is presented, using for the mule spinners' cancers the data given by Bridge and Henry, and a few cases from the literature were added to the list of mineral oil cancers recorded by the same investigators.

EXPOSURE TIME OF MINERAL OIL CANCERS (Bridge and Henry)

Years	11–15	16–20	21–30	31–40	41–50	51–60	over 60	Total
Mule Spinners' Cancers	9	17	54	107	104	55	6	352
Other Mineral Oil Cancers	8	4	18	18	8	4	0	60
Total	17	21	72	125	112	59	6	412

It may be emphasized that the above data, in regard to the length of exposure time, do not provide any exact information concerning the actual minimum time of contact necessary for the production of a cancerous response in man. It seems probable that the minimum time is definitely shorter than that listed in the table. This conception seems to be justified because the appearance of oil cancer was delayed, when the exposure was discontinued before the tumor became manifest or when the contact was interrupted for some time. Oil cancers with a delayed appearance following a relatively short exposure have been observed in men, who stopped working as mule spinners at an early adult age and drifted into other work. They developed many years later a

scrotal cancer (several tradesmen, a managing director, and a musician [Henry]).

XII. HISTOLOGY

a) Oil and Paraffin Comedones. The neck and duct of dilated hair follicles and sebaceous glands are obstructed by a cornified plug, which consists of a mixture of cornified matter, desquamated and necrotic epithelial cells, a few leucocytes, and some granular particles, representing paraffin or oil which entered these passages. The epithelial lining of these cystically distended follicles shows evidence of an active proliferation, particularly, in the region of the bottom of the follicle and in the external layers of the epithelial coat. Elongated cell pegs extend from these parts into the adjoining, edematous, connective tissue, which contains dilated and hyperemic vessels surrounded by sheaths of lymphocytes. The epithelial cells fronting the cystic lumina of the follicles possess an elongated, spindle shape. The cells in the deeper layers are more polygonal or cuboidal in shape and may exhibit nuclear, degenerative changes, cytoplasmic, fatty alterations, and a tendency toward an increased keratinization. Ullmann expressed the opinion that epitheliomas are derived from these hyperplastic proliferations of the follicular epithelium (folliculo-epitheliomas), whereas the surface epithelium undergoes a hyperplastic thickening, which is not progressive and does not assume a malignant character.

b) Hyperkeratotic Dermatosis. The surface epithelium is covered by a thick, cornified layer. In addition to these hyperkeratotic changes there exists an extensive, spotty acanthosis. The basal layer is irregularly outlined toward the cutis and contains atypical epithelial nests. Long and short, irregularly shaped or conical, solid epithelial processes extend from there into the subepithelial connective tissue, in which a dense, lymphoid infiltration is present. Epithelial anomalies are found in those parts of the skin, particularly, the skin of the scrotal sac, which are grossly normal apparently (Ackermann). This investigator noted that a relatively smooth and macroscopically unchanged skin, being remote from cancerous lesions, may contain intraepidermal, atypical foci and a highly irregular demarcation line between epidermis and cutis with small, focal keratoses in the epidermal thickenings and processes. The proliferative and atypical character of these lesions sometimes borders on malignancy. There are numerous ascending, newly formed blood vessels in the papillary cutis. While these epithelial manifestations are often accompanied by a round cellular infiltration in the cutis, such reactions may be entirely absent (Ehrlich). Similarly, hair follicles, sebaceous glands, and sweat glands may be free from any pathological changes in such regions.

Disturbances in the distribution of melanin represent a prominent feature of oil and paraffin skin. There occur foci with appreciable accumulations of a granular, brown pigment located in the rete layer, while adjacent parts appear entirely free from pigmentary deposits. Pigment granules may be found within the atypical, epidermal cell foci.

c) Paraffin and Oil Warts. It is necessary to distinguish between pseudo-warts and true warts. The pseudo-warts are, according to Ullmann, cutaneous folds of a swollen, edematous, and inflamed scrotal skin. The epidermis of such lesions displays a lack of abnormal or appreciable keratosis and acanthosis. As the perivascular, round-cell infiltations present in the cutis are free from bacteria, these cutaneous projections are considered results of a chemical irritation of the upper, cutaneous layers, causing an epidermal hyperplasia and cutaneous inflammation.

The epidermis of the true, papillomatous warts, found in the skin of the scrotum and other parts of the body, is thick, contains acanthotic, intraepidermal changes, and is covered by a broad, horny layer. The basal layer is often widened and composed of two or three rows of cells, among which peculiarly elongated cells are found. Solid, epithelial-cell pegs, sometimes consisting of atypical cells, which contain unusually large nuclei (evidence of disintegration) and numerous mitoses, extend at the base of the warts into the connective tissue. The connective tissue of the papillomatous cores and of the base is very vascular. A marked, inflammatory, round-cellular reaction of the stroma is a characteristic feature of these flat, palisade-like verrucosities, and distinguishes them from the ordinary warts. Sometimes, epithelial defects with ulcerations are observed.

d) Carcinomas. The warty excrescences with their epithelial abnormalities furnish one source from which epitheliomata may arise in the skin of oil and paraffin workers. Others may originate from epithelial hyperplasias and anomalies formed in the epithelial lining of the hair follicles. A third source of malignant developments in the skin of oil and paraffin workers is represented by primary, small, atypical, intraepidermal and epithelial foci. While the great majority of such proliferative lesions never advances beyond a rudimentary stage, a few of them take a progressive course and become carcinomas. They arise also abruptly within an apparently normal skin (Ehrlich). The epitheliomata produced by oil or paraffin are practically always highly cornified, squamous-cell carcinomas. The malignant growth is usually walled off from the surrounding, connective tissue by a broad zone of lymphocytes and plasma cells.

XIII. EXPERIMENTAL OIL AND PARAFFIN CANCER

The first attempts to reproduce paraffin cancer experimentally were made by Brosch (1900), who excised, in rabbits, a piece of skin of the interscapular region and applied repeatedly to this defect for three months a solution of paraffin in xylol. Brosch hoped that the production of a status of chronic irritation in connection with the epithelial regeneration might result in the development of cancer. The histological examination of the treated skin showed atypical, epithelial proliferations with cornified pearls resembling morphologically carcinomatous growth. In the production of these inflammatory and re-

generative epithelial proliferations the xylol, used as the solvent, plays an important causative role. Gawronski (1904) reported equally unsuccessful experiments in which dogs were employed. Ten years later Davis mentioned that he failed to elicit neoplastic responses in the skin of animals by the application of slack-wax and pressed distillate. In 1922, Leitch succeeded in producing cancers in the skin of mice after the repeated painting of various fractions of crude shale oil (green oil, blue oil, unfinished lubricating oil, and unfinished gas oil [the first three fractions mentioned contain paraffin]). Rats, guinea pigs, and rabbits, subjected to the same treatment proved refractory. Twort and Ing (1928) and Wood (1930), who applied various brands of purified, liquid paraffin to the skin of mice, did not elicit any neoplastic lesions.

Leitch reported in subsequent studies (1922, 1923, and 1924) the production of cutaneous malignancies in mice which had received applications of various refined oils obtained from shale oil and different types of petroleum, demonstrating that refined mineral oils, such as used for the lubrication of machinery, can cause cancer of the skin. Rats and guinea pigs treated similarly failed to develop cutaneous tumors. Rabbits showed only transient warts after eleven months of painting.

The most thorough and extensive experimental investigations of carcinogenic qualities of various mineral oils were conducted by Twort and Twort; Twort and Fulton; Twort and Lyth; and Twort and Ing. In a series of experiments, extending over a period of many years, these investigators demonstrated on large series of mice the carcinogenic property and potency of various crude and refined mineral oils obtained from naphtha and shale distillates. The results of these experiments were mentioned briefly before. As one of the by-products of these studies, Twort and Lyth developed a biological method for measuring the carcinogenicity of mineral oils. When 0.5 cc. of a certain mineral oil to be tested was injected intraperitoneally into mice, and the oil was recovered from the abdominal cavity one to 10 weeks later, and examined for its refractivity, the degree of reduction in refractivity ran parallel to the carcinogenic potency of the original oil injected. This reaction was related directly to the degree of unsaturation of the oil. Twort and Lyth attributed the decrease in refractivity of the oil, observed after its stay in the abdominal cavity, to the occurrence of chemical changes (reduction or oxidation).

The potency of a particular oil depends upon various factors (Twort and Twort): (*1*) the concentration of carcinogenic units in the agent; (*2*) the amount of the agent applied; (*3*) the nature of the diluent, if one was used (lanolin; purified paraffin oil; animalic and vegetable oils reduce the carcinogenic activity, while chloroform, benzol, and other organic solvents, which remove the natural fat of the skin, increase the carcinogenic activity of the oil tested); (*4*) possibly the area covered by the applications; (*5*) the total number of applications; (*6*) the frequency of applications; (*7*) the

susceptibility of the individual animal; (*8*) the general health of the individual; (*9*) the degree of natural oiliness of the skin; (*10*) hygienic and nutritional conditions; (*11*) perhaps the season of the year covered by the tumor-bearing period; and, (*12*) acquired resistance, immunity, and hypersensitivity. The number of tumors increased and the time of appearance decreased in direct proportion to the frequency of applications and the concentration and potency of the carcinogenic agent contained in the different oils.

Similar experiments, conducted by Wood (1930) with heavy American lubricating oil (Gargoyle "Mobile" Grade B, manufactured by the Vacuum Oil Company), showed that this oil, while strongly irritating to the skin of mice, did not seem to be carcinogenic. Only eleven out of 200 mice painted with this product developed benign papillomas after 113 to 240 days of treatment.

The results of these experimental investigations confirm the clinical observations made concerning the presence of carcinogenic qualities in a great number of crude and semi-refined oils, greases, and paraffins.

XIV. CAUSATIVE MECHANISM

At the time when the occupational oil and paraffin cancers were discovered, they were looked upon as the results of nonspecific, chronic irritations caused by the oils and paraffins (Volkmann and Tillmanns). Volkmann suspected the phenols in this respect; but Tillmanns, who made inquiries on this question in various soot, tar, and paraffin plants, came to the conclusion that phenols were not the irritating causative agents, but some other unknown substances. Eulenberg contended that naphthalenes were responsible for the carcinogenic action of oils and paraffins, in spite of the fact that Tillmanns had noted the non-irritative nature of these compounds. Acridin and substances of the anthracene and anthraquinone series were suspected by Leymann and Lewin. Green claimed that ammonium sulfate and sulfuric acid, contained in the oils, were responsible for the cancerigenic qualities displayed by these agents. Derville and Guermonprez considered the following three factors as possibly responsible for the cutaneous malignancies observed in workers of oil distilleries: irritative substances present in residues of the oil remaining in the retorts; caustic soda, which is mixed with the crude oil and remains, partly, in the coke formed; and the heat to which the workers are exposed when cleaning the retorts.

Ross expressed the opinion that the suspected, specific, chemical agent contained in the oil was not an irritant as it did not produce cell destruction, but cellular proliferation. This investigator pointed out that Cohnheim's theory of carcinogenesis from embryonally misplaced tissue germs was not in harmony with clinical facts regarding the characteristics of oil cancers. Southam and Wilson blamed the combination of the friction of the trousers, repeated

traumatism exerted by machinery, the action of dirt and sweat, and contact with the lubricating oil, for the development of mule spinners' cancer. Robertson asserted that this neoplasm was caused by the mechanical irritation from coarse overalls, traumatism caused by the machinery during the work, and a chemical factor furnished by the blue aniline dye contained in the material of the overalls worn by the spinners.

Scott claimed that the carcinogenic agent was present in the oil, but was not of nitrogenous nature, as the nitrogen-containing substances were removed during the processing of the oil and could not be responsible, for the same reason, for paraffin dermatoses and epitheliomas. This investigator emphasized that arsenic, suspected by Bayet as the causative factor, was not involved in the production of oil cancers, because arsenic was contained only in infinitesimal amounts (0.00056 per cent by weight) in shale oil and in still smaller quantities in blue oil (0.000015 per cent). The arsenic content of more refined oils was still lower, because of the treatment of the crude oils with sulfuric acid and soda during the refining process. Radioactivity of mineral oil as a cause of carcinogenic qualities, a concept later revived by Brockbank and Stopford, appeared to Scott as an improbable possibility, as many persons, in addition to workers in the oil and paraffin industry, come in contact with refined wax and burning oils without developing skin cancer. Scott proposed to give serious consideration to the organic sulfur compounds contained in the oils, as sulfides (thio-alcohols and mercaptans) were present in the crude, semi-refined and refined oils, and were found in considerable quantities in carcinogenic tars. Heller stated that the unsaturated hydrocarbons (olefins), contained in the unrefined oils, possessed strongly irritative qualities, which might cause epitheliomas. While the actual chemical agents responsible for the carcinogenic action of certain oils and crude paraffins have not been isolated, it seems likely that they belong to the same chemical type of substances which have been obtained from tar and pitch, that is, benzpyrenes and dibenzanthracenes.

Several investigators have pointed out that the degree, type, and character of the cutaneous reactions elicited by oils and paraffins depend upon the presence or development of a hypersensitivity response. Sträter and Kolesnikow noted that allergic reactions are involved in the production of oil and paraffin dermatoses. Kolesnikow observed that these cutaneous manifestations sometimes appear several months after the cessation of the contact with crude oils, as expressions of an existing hypersensitivity. Sträter stated that the results of patch tests demonstrated the existence of an allergic state of polyvalent nature and local character. Koelsch noted that the majority of oil and paraffin workers develops a certain degree of tolerance to contact with mineral oils; but some additional factor or combination of factors might elicit a sensitization of the skin, even after many years of well-tolerated exposure. Southam declared that idiosyncrasy plays a part in the development of mule spinners'

cancer. A similar opinion was expressed by Scott, who emphasized the importance of a "personal factor" of idiosyncrasic nature in the induction of cancerous reactions in the skin upon contact with cancerigenic shale oil.

XV. THERAPY

The therapeutic measures indicated in the management of oil and paraffin cancers of the skin are identical with those taken for the treatment of cutaneous cancers of the ordinary type. As these tumors remain local growths for a long time, surgical removal, especially of scrotal cancers, gives favorable and often permanent, curative results, particularly as an early detection and a radical removal of these accessible epitheliomas is relatively easy. The bilateral removal of the inguinal lymph nodes in cases of scrotal malignancy is advisable. Radium and roentgen-therapy is employed in most instances as a secondary measure for the prevention of recurrences following operative procedures. Papillomas, being potentially malignant, should be eradicated before ulceration occurs.

XVI. PRECAUTIONARY MEDICAL, SANITARY, AND TECHNICAL MEASURES

a) Medical. Pre-employment examinations should eliminate all applicants for work in oil and paraffin operations, who show congenital cutaneous abnormalities, such as ichthyosis, xeroderma pigmentosum, and similar cutaneous conditions. Periodical medical examinations of all workers directly or indirectly exposed to crude and refined oils in any form should be made approximately every three months. These examinations should represent an obligatory feature of the medical care of these workers, and their attendance should be compulsory for the employees of such operations. The examinations should be performed at even shorter intervals for those individuals who have shown evidence of precancerous, cutaneous manifestations, such as ulcerated warts and shagreen skin. Since an early diagnosis of neoplastic lesions represents the most effective guarantee for a good prognosis, physicians and workers should be educated to recognize suspicious early lesions. The workers should be definitely instructed concerning the dangers connected with the neglect or self-treatment of such manifestations (Somerford; Southam; and Bridge).

b) Sanitary. The workers must observe the utmost cleanliness of their body and clothes. Ullmann reported that in one paraffin plant the following rules are enforced: (*a*) all workers of presses must wash thoroughly at the end of the shift with tar soap, in order to remove the oil adherent to their skin; (*b*) working clothes are changed twice a week for clean ones, while the soiled clothes are washed in benzine; (*c*) a warm soap bath must be taken once a week; (*d*) workers who refuse to observe these rules are removed from the operation.

Twort and Somerford advocated the use of a mixture of lanolin and olive oil to be applied to the exposed parts of the skin as a protective measure,

reducing the direct contact of the skin with the mineral oil. Scott proposed, for the same purpose, the use of crude castor oil, as substances belonging to the paraffin series were insoluble in castor oil. The wearing of rubber gloves by especially exposed workers was recommended by Derville and Guermonprez. However, gloves made from natural rubber are rather easily penetrated by oil and deteriorate rapidly under its influence. It may be possible to manufacture gloves from certain types of synthetic rubber which may prove more satisfactory in this respect, as these synthetic products are rather resistant to oil.

c) *Technical.* Somerford stated that "the ideal means of preventing carcinomata among oil workers would be the substitution of an oil possessing all the necessary lubricating properties, but with the carcinogenic constituents removed." Similar requests have been made by Legge; and Bridge and Henry with the argument, that such a procedure represented the only effective means for the complete eradication of this type of occupational neoplasm. The painstaking work of Twort and his co-workers has done a great deal in showing methods by which this goal can be accomplished. These investigators recommended the following procedures for the reduction or destruction of carcinogenic agents contained in mineral oils:

(1) oxidation or reduction of oils,
(2) exposure to ultraviolet rays and radium emanation,
(3) treatment with sulfuric acid (Edeleanu process),
(4) treatment with sodium hypochlorite, and
(5) blending with non-carcinogenic mineral oils or saponifiable animal or vegetable oils, to obtain a dilution of the injurious oil below the carcinogenic level.

Through the importation of lubricating oils from other countries, which were used with the shale oils exclusively employed in the English textile industry formerly, there occurred in England, during recent years, a gradual change to a lubricating oil with a lower carcinogenic potency than previously (Henry). Although one of the suggestions made by Twort for the amelioration of a bad situation seemed to have been adopted, this development was not prompted by any desire of the manufacturers to introduce a measure preventing the further occurrence of oil cancer among their employees(Henry). Certain improvements made recently in the production methods of oils and paraffins, and in the machinery and manufacturing techniques of industries which use lubricating oils, have tended to decrease the formerly existing hazard (introduction of refrigeration method and centrifugal separator method in the paraffin industry; and replacement of mule-spinning by ring-spinning). But progress in this field appears to be very slow. In 1937 Twort and Twort wrote in an English trade journal, "Little has been done in the past five to ten years in the direction of making carcinogenic lubricating oils less likely to induce inflammation or carcinoma." The morbidity and mortality statistics of oil and paraffin cancer in England bear out this statement.

XVII. MEDICO-LEGAL ASPECTS

Epitheliomata of the skin, caused by occupational contact with mineral oil and paraffin, are included among the compensatory, industrial diseases of many countries [Argentina, Australia (West Australia and Queensland), Belgium, Cuba, Great Britain, Ireland, Rumania, Venezuela, Germany, Russia, and Mexico], and a number of states of the United States (California, Connecticut, District of Columbia, Illinois, Indiana, Massachusetts, Missouri, New York, North Dakota, North Carolina, Wisconsin, Ohio, Pennsylvania, Rhode Island, and Washington).

The scrotal cancer of mule spinners is covered in England by special legislation. In none of the countries mentioned do there exist laws which include primary malignant tumors of the internal organs (lung, gastro-intestinal tract), which arise occasionally simultaneously with or successively to cutaneous cancers, among the notifiable and compensatory industrial neoplasms caused by oil or paraffin in spite of the fact that they may become more likely to be the actual cause of death than the readily accessible cutaneous manifestations (Southam). It may be advisable to recognize such obvious etiological relations in framing future compensation laws so as to obviate evident inconsistencies and injustice in the application of the law.

Finally, mention may be made of the possibility of the occurrence of acute traumatic oil cancers which should find proper consideration in the practical application of compensation law. Barkmeyer reported, for instance, the development of a cancer of the face in a 53 year old female spinner, who had sustained an accidental lesion of the face when lubricating oil sprayed into her face during the work. The compensability of the ensuing neoplasm was denied by the Swiss compensation board. Similar accidental lesions of more serious character are apt to occur in connection with workers around Diesel engines, in which a fine stream of oil is ejected from a jet under high power and may penetrate deeply into the tissue.

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d. CREOSOTE

Creosote is a fractionation product of wood or gas tar which distills over between 210° and 280°C and which is extensively used in industry for various purposes (wood preservative: wooden paving blocks, railroad ties, telegraph poles, shingles, props in mines; preparation of lysol; manufacture of oil pressed bricks; sheep dip; Diesel engine and furnace fuel). Individuals exposed to an occupational contact with creosote oil are workers employed in tar distilleries; men engaged in the pickling of timber; railroad workers, miners, and carpenters who handle creosoted wood; brick, tile and pipe pressers using creosote oil for the lubrication of die molds; farmers using creosote oil for dipping; Diesel engines' engineers and delivery men of this fuel; attendants of furnaces in glass works, steel works (heating of rivets) (Bridge and Henry; O'Donovan; White; Heller; Hope; and others). During some of the operations mentioned (pickling of timber for waterproofing), *hot creosote* is used. Splashes of creosote are received during this and other operations on the face, forearms and hands and, at the same time the trousers are soaked with creosote oil, exposing thus indirectly the anterior aspects of the thighs and the scrotal region to this substance.

Mackenzie (1898) reported from England the first case of scrotal papillomatosis suspected of malignancy of the skin in a pickler of railroad ties, while Legge observed eczematous eruptions on the forearms of men using creosote for the lubrication of die moulds in brick factories (Kennaway). In 1920 O'Donovan recorded the first and definitely established cases of creosote epithelioma in four picklers of timber. These cases were seen by O'Donovan from 1902 to 1920 in 16 cases of occupational skin cancer. Cookson added one more case of creosote carcinoma in 1924. Bridge and Henry, in 1928, noted ten additional cases of this industrial neoplasm, six of these being present in brick,

tile and pipe pressers, while four were found in creosoters of wood. The most recent report of neoplastic, papillomatous reactions to creosote came from Haldin-Davis in 1935.

After Hudelo, Rabut, Cailliau and Mornet noted in 1929 the occurrence of melanosis in a railroad worker who had handled creosoted sleepers, Laborde, Huguenin and Boucabeille reported three cases of creosote carcinoma and a second case of creosote hyperkeratosis in brick pressers in France (1935). Similar observations were made in recent years in Germany. In 1930 Epstein listed creosote cancer among the professional malignancies of the hands and, during the following year, a case of creosote cancer in a man who treated railroad ties with carbolineum was placed on record by Jacoby. McCafferty, in 1927, mentioned the presence of melanoderma in creosote workers in the United States. Heller, however, did not find any tumors, but only burns in twenty men employed in a plant creosoting railroad ties in Pennsylvania (1930). Of the twenty creosote epitheliomas of industrial origin placed on record, sixteen were observed in England, three in France, and one in Germany. It is important to note in this connection that Laborde, Huguenin and Boucabeille stressed the high incidence of this type of occupational cancer about which there is so little information.

Prolonged contact with creosote causes, first, the development of a dermatosis characterized by the appearance of roseous macules and papules, verrucous hyperkeratoses and warts, scattered telangiectases and pigmentary disturbances. While White stated that melanosis was associated rarely with these cutaneous manifestations, other investigators mentioned melanotic spots as well as localized leucoderma as rather regularly observed lesions. The hyperpigmentations are often circumscribed and perifollicular, sometimes deep brown black in color and located in the face, volar aspects of the forearms, scrotal region and knees. The warts are usually multiple and develop after a prolonged period of exposure. Many of the warts regress spontaneously, fall off and leave scars. Some of these lesions, however, progress into epitheliomatous growths which ulcerate, proliferate slowly into neoplasms of large dimensions and, ultimately, may form metastases in the regionary lymphnodes and remote organs, thus causing death. The carcinomas are histologically cornified spinous cell cancers. Multiplicity of the neoplastic reactions was noted in two instances (Jacoby; O'Donovan) (scrotum, penis, arms and knees; face and forearm). The majority of the cancers affected the scrotum (16); two were found involving the penis; three the forearm and one the face. The age of the workers was stated in six cases (4 cases: 51 to 60 years; 2 cases: 61 to 70 years). The relatively high age observed (55 to 65 years—Cookson; Epstein) is attributed to the long exposure time necessary for eliciting a cancerous response to creosote. Of seven cases, three had been exposed for 15 to 20 years, two cases for 21 to 30 years and two cases for 31 to 40 years.

Sall and Shear produced epitheliomas in the skin of mice painted with the basic fraction of creosote oil in benzene.

Creosote epitheliomata are in most countries included among the compensable occupational diseases resulting from exposure to derivatives of tar (Carozzi).

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e. ANTHRACENE

Anthracene is a component of the "anthracene oil" which is obtained when tar is distilled at a temperature of 230°-270°C. A crystalline mass settles out from this oily substance upon standing. This solid fraction, being about 5 per cent of the total consisting of a greenish material strongly smelling of creosote, is centrifuged out and then compressed into cakes (anthracene cakes) that contain the crude anthracene. The oily portion (green oil) is composed of volatile hydrocarbons, phenols, anthracene and its homologues. The solid matter is called "40 per cent anthracene". After having been shipped to the anthracene factory, the anthracene cakes are broken down by hand, ground, and subjected to a refining process, during which the material is exposed to steam, washed with solvents (naphtha mixed with pyridine bases) in which anthracene is soluble. The resulting 85 per cent anthracene is then distilled with potash and lime, washed with solvent naphtha, sublimed, finally appearing as an odorless, bluish white, fluorescent, scaly, crystalline matter which melts at 213°C and which is an isomer of phenanthrene. The material re-

moved during the refining process consists mainly of carbazoles, acridine and many other substances (anthracene residue).

Anthracene oil and green oil are used in the manufacture of lubricating grease by mixing 86 to 88 per cent of the heavy oil, sometimes receiving an addition of creosote, 4 to 7 per cent rosin oil, 4.5 to 6.5 per cent slaked lime and water. Heat is evolved when lime is added to the mixture causing the splashing of the hot liquid. Anthracene oil is employed as fuel for Diesel engines, as an absorbent in the washing of gas, and as a lubricant for the clay moulds in brick making, while the grease serves for the lubrication of wire ropes on ships and in mines. Crude anthracene oil finds use in the form of carbolineum as a paint and preservative of timber, for the water proofing of wood and for making briquettes. The refined anthracene is employed in the manufacture of anthraquinones and alizarin dyes.

Workmen exposed to contact with crude anthracene are men employed in anthracene plants, especially those attending centrifugal machines, hydraulic and filter presses, and purifiers as well as all workers pressing the anthracene cakes, handling the anthracene cakes (yardmen), and grinding the cakes (White; O'Donovan; Leymann). An occupational carcinogenic hazard exists also for the employees of grease factories in which anthracene or green oil is used, particularly for those working as mixers (Kennaway; Oliver; Legge; Sträter). Contact with purified anthracene appears to be innocuous (White; O'Donovan).

The first cases of occupational anthracene epithelioma of the skin were reported by Leymann (1917), who noted that in a 1902 annual report issued by chemical plants located in Oppeln, Silesia, mention was made of the occurrence of warts, hyperkeratoses and eczemas of the hands, arms, feet, knees, neck, chest and back, in 22 out of 30 workers employed since 1892 in an anthracene plant, and that surgical operations, apparently for scrotal cancer, had been performed on three of these workers, who had been in these anthracene operations for 6 to 8 years (Koelsch; Sträter). Rambousek, in 1913, mentioned that contact with crude anthracene oil occasionally gives rise to epithelioma.

Oliver in 1908 recorded the occurrence of anthracene epithelioma in two workers of a grease factory in England. Twelve years later O'Donovan noted the occurrence of four additional cases of this type of industrial neoplasia in workers of an anthracene and alizarin plant, between 1903 and 1920, after Legge had observed previously an additional case of epithelioma in a grease maker (Kennaway). Bridge and Henry mentioned four cases of epithelioma in anthracene workers. There is thus a total of 19 cases of anthracene epithelioma on record. No new case has been reported since 1921.

Anthracene being a photosensitizing substance causes in anthracene workers first an acute erythema developing upon the exposure to solar radiation (Weider; Grincar and Rachmanow). Similar attacks may occur repeatedly

during the sunny season. With prolonged and continued contact with this chemical, there appears an excessive pigmentation of the skin, especially of the face, forearms and neck which produces a bronzed, dark, swarthy complexion. The hands have a deep brown and, occasionally, a greenish color. Small, pink telangiectases and numerous, minute, grey, hard keratoses are formed on the face and forearms, affecting mainly their ulnar aspects. Small, white, round scars result when these cutaneous manifestations regress. Comedones also exist. The malignancies start in the keratotic warts, which may ulcerate and form fungating or button-like firm masses. The cancers are histologically cornified squamous cell carcinomas. The incidence of such a transformation may be estimated from the statements of Leymann (three cancers among 30 workers) and of O'Donovan (3 epitheliomas among 25 workers). The cancers observed were solitary. They grew, in general, slowly and did not form readily metastases, but caused death in several instances.

The ages were recorded in six cases (33, 62, 53, 72, 38, and 59 years). The exposure time for these instances was 17.5 (with 25 years previously exposed to pitch), 30, 42, 23, and 32 years. The carcinoma was located, in one instance, on the back of the hand; in one case in the region of the wrist; in three cases on the forearm; in one case on the cheek; and in four cases on the scrotal sac.

The experimental production of anthracene cancer by the repeated application of anthracene oil dissolved in xylol to the skin of mice was attempted unsuccessfully by Jordan. Kennaway demonstrated subsequently that anthracene oil as well as green oil caused the development of malignancies when painted upon the skin of mice in a few of the animals thus treated. The chemicals proved to be highly toxic to mice, so that only a few mice survived sufficiently long for the development of malignant responses. There were, on the other hand, no tumors in two series of mice which received applications of 40 per cent anthracene and anthracene residue, respectively. Kennaway concluded from the experimental evidence obtained that the cancer producing substances are not present in any appreciable amount among the solids in suspension in the anthracene oil.

Grincar and Rachmanow recommended to exclude workers with seborrhoea, excessive perspiration, recurrent eczema, congenital or acquired photosensitivity or a dry, pigmented skin from employment in anthracene operations. Leymann mentioned that the occurrence of the anthracene dermatoses and malignancies in German plants was followed by the introduction of these sanitary and technical preventive measures: The workers were supplied with special clothes that fitted tightly around the neck and wrists. These garments were cleaned and exchanged for fresh ones every week. The workers were obliged to take a warm bath at the end of the shift. The clothes used in the cake-presses were laundered mechanically, thereby abolishing the exposure of female workers, used for this purpose, to anthracene.

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f. SOOT. I. CHEMICAL AND TECHNOLOGICAL ASPECTS

Soot is the product of the imperfect combustion of highly carbonaceous substances, such as coal, mineral oil, pitch, tar, resins, wood fats, vegetable and animal oils, and combustible gases. It is a deep black pigment in a very finely divided state, consisting mainly of carbon with an admixture of hydrocarbons. Soot represents an incidental by-product from burning of coal, wood, and other kinds of carbonaceous fuel in furnaces, stoves and, especially, in fireplaces in which the draft is deficient and combustion is imperfect. The soot thus formed is precipitated in part in the chimney and on its walls. Soot or lamp-black is manufactured in large scale operations by subjecting mineral oil, tar, pitch, and resins to incomplete carbonization. The substance finds employment for many industrial purposes, such as the manufacture of printing inks, oil paints, India ink, shoe black, explosives, black lacquers and, formerly, as a snail poison in gardening (Martineck; Oppenheim; Ullmann; Oliver).

Occupational exposure to soot or lamp-black exists for chimney-sweeps, stokers, smiths, workers employed in lamp-black factories (soot burners, packers, loaders), printers, paint manufacturers, shoe polish makers, workers of explosive plants (firecrackers), gardeners, and others.

II. HISTORICAL ASPECTS

Cancer of the skin, resulting from an occupational contact with soot,

occupies a unique position among the various types of industrial malignant neoplasms for several reasons. Soot cancer of the skin is the first malignant tumor of definitely occupational origin, being described in 1775 by Percival Pott as the chimney-sweeps' cancer of the scrotum. This type of industrial malignant blastoma is also the first one which has been made the subject of a legislative action of a preventive and supervisory character. The first laws regulating the activities of the chimney-sweeps' trade were passed in England in 1788 and were intended to curtail the existing occupational hazard. The early scientific and legal attention, which this neoplasm received, continued until rather recent years and resulted in one of the most thorough and detailed investigations of the various aspects made in connection with different industrial cancers.

III. GEOGRAPHICAL DISTRIBUTION AND INCIDENCE

After the communication of Pott there appeared in England during the following decades a considerable number of reports on the subject of soot and chimney-sweeps' cancer [Bell (1794); Earle (1808); Simmons (1808); Wadd (1817); Aldis (1820); Earle (1823); Henry (1828); Cooper (1830); Hawkins (1838); Curling (1845); Dixon (1850); Paget (1850); Lawrence (1850); Milton (1860); Paget (1863); Lawson (1878); Heath (1883); Butlin (1889 to 1892); Spencer (1890); Newsholme (1899); Legge (1902); Oliver (1908); Morley (1911); Crow (1914); Southam and Wilson (1922); Leitch (1924); Bedford (1930); Henry and Irvine (1936); Henry (1937); Kennaway and Kennaway (1937)]. No reliable data are available concerning the incidence of soot cancer among the chimney-sweeps in England for the early part of the past century. Fütterer found 47 lethal cases of this type of occupational cancer recorded in the English literature between 1808 and 1854. Butlin collected, for the years 1880 to 1882, 23 cases of scrotal cancer among chimney-sweeps. At the turn of the century chimney-sweeps' cancer of the scrotum still represented the predominant type of scrotal malignancy observed in English hospitals. There was observed in St. Bartholomew's Hospital, London, 29 cases of sweep's cancer among a total of 39 scrotal cancer treated during 1880 to 1890. In the period of 1910 to 1912, 23 out of 107 deaths of chimney-sweeps were caused by scrotal malignancy. Kennaway noted, for the same period, 16 fatalities from scrotal cancer in 65 deaths of chimney-sweeps, while Leitch mentioned for these years the occurrence of only 7 fatal cases of chimney-sweeps' cancer of the scrotum in a total of 16 fatalities from scrotal cancer. The same investigators recorded 10 cases of scrotal cancer in sweeps in 1921 to 1922, and 4 cases for 1923. Kennaway and Kennaway prepared for the period 1910 to 1923 the following incidence table of cutaneous malignancy among chimney-sweeps in England and Wales:

INCIDENCE AND DISTRIBUTION OF CHIMNEY-SWEEPS' CANCER

Year	Head and Neck	Arm, Hand, Trunk, Foot, Leg	Penis	Scrotum
1910–1912	0	0	1	16
1913–1914	2	0	1	7
1921–1922	data not available		2	10
1923	0	0	1	4

Henry analyzed the fatalities from scrotal cancer in England and Wales during the years 1911 to 1935 in their relation to occupation and found that among a total of 1,747 cases 103 were present in chimney-sweeps (6.9 per cent). These occupational cancers were divided as follows upon the quinquennial period: 1911-1915: 22 cases; 1916-1920: 20 cases; 1921-1925: 25 cases; 1926-1930: 17 cases; 1931-1935: 19 cases.

While the absolute figures on chimney-sweeps' cancer of the skin are not very impressive when compared with those recorded for mule-spinners' cancer, which also most often attacks the scrotal skin, consideration must be given to the fact that there is a much smaller number of chimney-sweeps employed than mule-spinners. Data concerning the relative incidence of chimney-sweeps' cancers have been recorded by several investigators. Legge, during 1910-1912, stated that 29 per cent of the deaths of chimney-sweeps were caused by scrotal cancer compared with 1 per cent from this cause in the general population. Kennaway and Kennaway, who determined the incidence of scrotal cancer in England and Wales for the years 1911 to 1935, noted 100 cases of fatal scrotal cancer among 5,274 sweeps, while the total number of deaths from scrotal cancer among the male civil population over twelve years of age (13,901,108) in this period was 1,486 cases, of which only 888 were nonoccupational. Leitch estimated from the incidence figures of scrotal cancer among sweeps during the years 1910-1912, 1921, and 1923 that there died 4.6 sweeps every year from this disease, or, as the total number of sweeps in England and Wales was 5,251, one sweep out of 1,140 died every year. The excessive incidence of scrotal cancer in chimney-sweeps is reflected also in an observation of Kennaway, who found that in years 1911-1912 one out of every four deaths caused by cancer in chimney-sweeps was due to a scrotal malignancy, while the ratio for the general population was one scrotal cancer to 560 cancers of all organs. This investigator stated that there was no evidence that chimney-sweeps' cancer had become less frequent during 1910 to 1923. This condition seems to have continued during the following years, as Henry found that the crude death rate from scrotal cancer in chimney-sweeps was the same during the quinquennial periods 1911-1915 and 1931-1935. A similar result was reported by Henry and Irvine

when they analyzed the cases of scrotal cancer which occurred during 1837 to 1929 in the Blackburn Registration District. While the incidence ratio of scrotal cancer deaths in sweeps to total number of employed sweeps was 308 per 1,000, this ratio was found to be for the occupationally not predisposed part of the general population, 0.2 cases of scrotal cancer to 1,000 employed individuals.

Attention must be called to the fact that statistical evidence supplied from English sources covering a period of approximately 75 years indicates that sweeps display not only an excessive liability to cutaneous and particularly scrotal cancer, but also to cancer in general. Newsholme thus noted in a statistical analysis of the cancer mortality in England during the years 1861-1890 that chimney-sweeps exhibited the highest cancer death rate among all occupations studied (156 per 1,000 deaths compared with 36 per 1,000 deaths in miners). An even higher cancer death ratio among chimney-sweeps was found by Butlin for the years 1880-1882 (202 cancer deaths per 1,000 deaths against 36 cancers deaths per 1,000 deaths in the general population). Legge calculated the cancer death rate for sweeps from 25 to 65 years old for the years 1900-1902 and noted that it was 133 per 1,000 deaths in sweeps compared with 63 per 1,000 deaths in the general population. Similar data were given by Tatham, who noted a cancer death rate for sweeps of 156 per 1,000 and, for the general population, of 44 per 1,000, adding that the cancer liability of sweeps was eight times that of the general population. Hope's statements on this subject, covering 1900-1903, were practically identical with those recorded by Legge (cancer death rate of sweeps, 131 per 1,000; cancer death rate of occupied male population, 68 per 1,000).

Collis and Greenwood's assertion that there was a decrease in cancer deaths among chimney-sweeps, amounting to 40.6 per cent during 1900-1902 in comparison to the period 1890-1902, is not supported by the observations of all other investigators, who analyzed the same or closely related periods. Kennaway called attention to the fact that 40.8 per cent of the nonscrotal cancers of chimney-sweeps found among a total of 65 fatal cases (1910-1912) involved the respiratory and alimentary tract above the stomach, that is regions, in which in general only approximately 25 per cent of the total number of cancers are situated [16 scrotal cancers, 1 cancer of penis, 1 of inguinal nodes (18 typical chimney-sweeps' cancers); 6 cancers of tongue, 4 cancers of pharynx, 3 cancers of jaw, 3 cancers of esophagus (16 cancers of upper alimentary tract); 1 cancer of the lung, 2 cancers of the larynx (3 cancers of the respiratory tract); 10 cancers of the stomach, 6 cancers of the rectum, 6 (!) cancers of the liver (22 cancers of the lower alimentary tract); 1 cancer of the kidney, 1 cancer of the bladder, 1 cancer of the prostate, 2 cancers of the testis (5 cancers of the urogenital tract].

Kennaway is convinced that these differences in the topographical distribu-

tion of cancers in sweeps from that generally observed are significant. Cusack reported a single case of soot cancer from Ireland (1847), while Butlin claimed that chimney-sweeps' cancer was unknown in Scotland [Syme (1835)].

While the evidence presented demonstrates that soot cancer of the skin, and probably as well as some of the internal organs still represents an important occupational health hazard in England and Wales, these industrial neoplasms did not play at any time a significant rôle in the European continent and in the United States.

The first communication on the subject from Germany was published by Stöhr (1882), who referred, however, exclusively to the occurrence of chimney-sweeps' cancers in England. Subsequent reports dealing with chimney-sweeps' cancer appeared from this country in great intervals and described individual cases [Krohn (1826); Altmann (1827); Kohler (1835); Mohns (1876); Junginger (1889); Roser (1886); Baum (1874); Richter (1930); Dütschke (1931)]. Baum stated, according to Butlin, that chimney-sweeps' cancer made its appearance in Hannover after 1874, that is, twelve years following the more extensive use of coal in place of wood for heating purposes. When Richter in 1930 asserted that not a single case of chimney-sweeps' cancer had been recorded in Germany during the preceding 40 years, Dütschke reported an instance of this industrial neoplasm observed by him during more recent years. Nevertheless, chimney-sweeps' cancers were always rare in Germany and were exceptionally so during more recent times.

Similar conditions seem to prevail in France. While Mérat (1820); Marjolin (1828); Nélaton (1850); Lebert (1851); and Bang (1927) wrote on this subject, none observed a case of this industrial cancer. It is stated that Selle (1787) as well as Alibert (1817) saw several cases among the chimney-sweeps of France. It seems to be doubtful, whether or not any instances of this occupational neoplasm have been observed in Belgium [Anciaux (1816); Zoude (1841); Butlin (1892)]. This applies to Denmark [Hannover (1852); Bang (1927)], Sweden [Sandberg (1903)]; Austria, Italy, and the United States [Warren; Haagensen (1933); Carozzi (1934)]. The occurrence of a single case of chimney-sweeps' cancer in Norway was recorded by Guldberg (1927), after Gade had contended in a publication appearing in the same year that no tumor of this genesis had been observed in this country. Kocher quoted Rouges as seeing several cases of sweeps' cancer in Switzerland. A report of Krzykowski (1876) mentioned the occurrence of inflammatory ulcers in sweeps in Poland.

IV. EXPOSURE

The marked and striking numerical discrepancy existing in the incidence of chimney-sweeps' cancer in England and in all other countries has been the subject of numerous studies and speculations. There seems to be a combination of several reasons of chemical, technical, architectural and social nature which accounts for this peculiar phenomenon in England.

1) The type of coal used in England for heating purposes differs chemically from that employed in other countries. Leitch stated that the carcinogenic agent responsible for the production of chimney-sweeps' cancer is contained in the soot produced by coal mined in the Midlands of England, where a bituminous hard coal occurs. This coal was used extensively in England for the heating of houses during the latter half of the 18th century, while it became customary elsewhere at a later date, to employ pit coal for such purposes (Hope).

2) In addition to the difference in the chemical composition of the types of coal used in the various countries, consideration must be given to the fact that coal was burned in England to a large extent on open grates in fire-places which developed a great deal of soot because of insufficient draft (Butlin). Kennaway has pointed out that the cancerogenic qualities of soot depend, apparently, upon its content of tar and that this factor is directly related to the intensity of the draft and the degree of temperature under which the coal is burned (Cohen and Ruston). The soot produced by a kitchen stove having normally a strong draft contains, according to Kennaway, for this reason less tar, than that found in the chimney of a fire-place of a dining room. Analyzing the soot from various sources for its tar content, Kennaway made the following observations to bear out his contentions:

Original coal	*Tar* 1.64 per cent	*Tar* 0.88 per cent
Kitchen flue soot	12.50	25.90
Dining room flue		
5 feet from grate	34.40	
35 feet from grate	30.40	
Boiler chimney 110 feet high		
5 feet from bottom	0.09	
top	1.14	

The tar was obtained from the coal and from the soot by ether extraction. It was found that the tar content of the soot stands in inverse proportion to ash residue. It is stated that not all types of soot possess carcinogenic qualities. The soot produced by the combustion of wood and of Scottish coal is said to lack such properties (Bell).

3) Structural peculiarities of the English chimneys, especially those of older houses, represent doubtlessly important contributory factors in the production of soot cancer by influencing the intensity, duration and degree of exposure to the carcinogenic soot, as they favor the deposit of soot in the chimney and necessitate a technique of cleaning that requires intimate contact of the sweep with the soot.

The English chimneys in an earlier day were relatively wide (30 to 60 cm. in diameter), very irregular and tortuous in their construction, often running horizontally for some distance and thus permitting in such parts the accumulation of considerable amounts of soot. The chimneys of this type could not be cleansed from above by the introduction of brushes or scrapers, but had to be cleaned by hand. The sweeps were forced to enter the chimney, for loosening the soot from its walls and for the removal of the soot from its passages. The so-called "climbing boys"

who were children of the age of four years and older during the times of Pott were used for this work in the narrow quarters.

It is obvious that such operations entailed a very intimate and massive contact of the skin with the soot, which was often intensified by the simultaneous action of the heat from the walls and by mechanical trauma from friction and abrasions sustained during the work. Chimneys in more modern English houses were built, on the other hand, according to the continental pattern, that is, they were narrower and straight (30-40 cm. wide in Germany, 25-30 cm. in Russia and eastern Europe [Baader]) and were entered either from below through the fire-door at the base of the chimney or from above, and were cleaned with the aid of a root-broom which was lowered into the chimney on a chain having an iron ball attached to its one end. This technique, which was followed also in Scotland, according to Liebe, necessitates a much less intense contact with soot and moreover is not complicated by thermic and mechanical traumas to the sweeps.

4) Differences of hygienic, social and personal nature had evidently a part in producing the excessive incidence of chimney-sweeps' cancer in England. Butlin pointed out that the sweeps in Belgium and northern Germany not only observed a higher degree of personal cleanliness than their English colleagues, but they were wearing also some kind of protective clothing, which fitted tight around the neck, wrists, and ankles and thus reduced the exposure of the covered skin to soot. It is evident that protective measures of this kind, combined with frequent and thorough cleansing of the exposed parts, decreases appreciably the intensity as well as the duration of exposure and thus may eliminate, to a large extent, the carcinogenic hazard.

It appears to be very probable from the information available that these factors contributed to a considerable degree to the high frequency of sweeps' cancer in England, as it was customary in this country to employ during the latter part of the 18th century and the first half of the 19th century young boys for the climbing of the chimneys, until this abuse was ultimately more or less stopped by legislative measures. Bang as well as Butlin gave a vivid description of the pitiful life and the abominable working conditions of these children who started their careers at the early age of four years in many instances. They came from the poorest social class and were often sold into this work by their parents. Ill fed, badly dressed and miserably treated, they had for bedding not infrequently only the bags which they had filled with soot. It is quite obvious that children of such a tender age and coming from a social strata where personal cleanliness cannot be expected to be a well-developed habit could not be expected to have the urge to free their bodies from the soot at the end of a day's work even if washing facilities had been available to these poor creatures. Chimney-sweeps of those days who had survived the hardships of an apprenticeship had thus a relatively long occupational exposure to soot even when still young.

The employment of children as apprentices was customary during the past century also in several continental countries (Bang). They were recruited

in France and Italy usually from Auvergne and Savoie. During the summer time they roamed in groups through the countryside similar to the English climbing boys and returned in winter to the cities for work. Boys, seven years of age, were entered as apprentices in Belgium, and boys 14 to 15 years of age served in this capacity in Germany, where some chimneys in older buildings had to be climbed. Similar conditions prevailed during the early part of the last century in Denmark, where usually Swedish boys were used in this profession and, occasionally, had to climb chimneys.

An analysis of these data indicates that, inasmuch as chimney-sweeps' cancer is a frequent occupational disease in England even in modern times under improved working conditions, hygienic precautions and governmental and medical supervision and control, the chemical composition of the coal used as well as the production of a soot rich in tar represent the main causative factors, and account mainly for the high incidence of this industrial neoplasm among the chimney-sweeps of England and Wales.

The carcinogenic properties of soot are attested also by the occurrence of skin cancer in members of occupational groups other than sweeps. Bell mentioned the presence of epitheliomas in soot workers. Earle reported the development of a cancer on the left hand in a gardener who used soot as a snail poison. A second case of soot cancer of the hand (of a woman) was recorded by Cussack. Paget saw a cancer of the external ear in a man who used to carry bags filled with soot on his shoulder. Fischer cited Will concerning the occurrence of cancer of the feet and toes in women who stamped soot with their bare feet in a soot factory. Oppenheim noted the presence of warts and of an ulcerated node on the ear in a soot burner.

V. AGE

In analyzing the data recorded by the various English investigators, it becomes evident that there has taken place a marked shift in the average age into the older age groups for persons affected with soot cancer during the course of the last 150 years.

Earle (1823) and Curling (1866) stated that the average age of the chimney-sweeps with scrotal cancer was from 30 to 40 years. Earle, however, observed 3 cases of scrotal cancer in sweeps who were 20 to 30 years old. Inasmuch as up to 1842, apprentices, 4 to 10 years of age, were started in this profession, sweep-cancer was seen occasionally at a much earlier age during the first half of the past century. Pott observed a sweeps' cancer in a climbing boy 8 years old and Wadd found such a neoplasm in a boy 15 years of age. Cooper operated on a boy 16 years old for a cancer involving the scrotum, penis and pubic region, that is, a tumor of relatively long standing. Another of Cooper's cases was 22 years old. Hannover mentioned a sweep, 18 years of age, who had suffered from scrotal cancer for seven years previously.

When Butlin (1892) studied the age distribution of the 29 cases of sweeps'

cancer which he had studied during the preceding 20 years, he found that the average age was from 45 to 50 years, that is, an increase of 10 to 15 years when compared with that noted by Earle in 1823. In the meantime the age for apprenticeship had been increased by law to 16 years (1842).

Butlin gave the following age distribution of his 29 cases:

Years	25–30	30–35	35–40	40–45	45–50	50–55	55–60	60–65
Cases	2	2	2	5	10	4	2	2

Henry, who investigated the age factor in chimney-sweeps' cancer for the period 1911 to 1935, found that the average age at death from this industrial neoplasm for the years 1911 to 1915 was 58 years; and for the years 1931 to 1935, 65.8 years (an increase of 7.8 years); while for the entire period 1911 to 1935, 61.9 years. This figure compares well with the average age of persons dying from scrotal cancer of unknown etiology which was, according to Henry, in 199 cases 57 years. Henry concluded from the evidence available that the remarkable extension of life expectancy of sweeps' cancer can be accounted for to a great extent by the simultaneous shift of the beginning of the exposure period into older age groups and by improved technical, personal and sanitary conditions which were gradually introduced during more recent times. The earlier institution of more successful therapeutic measures during the last five decades contributed doubtlessly to this development. The age distribution of the chimney sweeps' cancers in Henry's series was as follows:

Years	30–35	35–40	40–45	45–50	50–55	55–60	60–65	65–70	70–75	75–80	80–85
Cases	1	1	5	12	6	14	19	15	13	9	8

Henry mentioned that death from scrotal cancer in sweeps under the age of 35 years is now rare (less than 1 per cent of the total number during the 25 years' period). Whereas Henry considered death from cancer of the scrotum in sweeps under 40 years as rare, Thachrah stated in 1941 that many sweeps die while still young and few live to the age of 50.

The data available to Henry did not supply any information concerning the exposure time present in his series. Henry noted, however, that deaths from cutaneous malignancy among sweeps before the age of 45 years was always attributable to a scrotal cancer, whereas from then on also skin cancers of other sites occurred and caused death. The percentage of deaths from scrotal cancer in relation to the total death rate from cutaneous malignancy rises, on the other hand, up to the age group 55 to 64 years, but declines

with the more advanced age groups. The following table of Henry illustrates these relations.

AGE DISTRIBUTION OF SCROTAL AND EXTRASCROTAL SWEEPS' CANCERS (Henry)

Site Years	25–35	35–45	45–55	55–65	65–75	75–85	85–95	Total
Scrotum	1	6	18	33	28	17	—	103
% of total	100	100	72	78.6	63.3	63	—	70
Extrascrotal	—	—	7	9	13	10	5	44
% of total	—	—	28	21.4	31.7	37	100	30
Total	1	6	25	42	41	27	5	147

The evidence presented shows quite clearly that the manifestation age of chimney-sweeps' cancer is directly dependent upon the age at which the occupational exposure to soot begins (Kennaway; Bang) and is entirely unrelated to any hypothetical senile changes of the skin. Intensity and duration of exposure to soot represent additional important factors which influence the manifestation time (Leitch).

VI. SYMPTOMATOLOGY AND PATHOLOGY

The skin of the exposed parts of the body as well as of the scrotum which are more or less covered with soot becomes dry and seborrhoic. Soot outlines the fine folds of the skin and is present particularly in the depth of the rugae of the scrotal sac, where black plugs obliterate the openings of the excretory ducts of the sebaceous glands. These changes are followed by the development of small, but usually numerous warts which may cover densely the genital region (Paget). These papillomatous formations may persist for months or even years without undergoing any further changes. However, some may become fixed at their base in the course of time and may ulcerate later. The edges of these ulcerated epitheliomatous defects are elevated, firm and indurated, while a fetid, serous material exudes from the ulcerated surface. The ulcer and the surrounding indurated area gradually spread, often form vegetative excrescences, and may finally involve the testes, spermatic cord, penis, large femoral vessels and inguinal nodes. The cancerous growth may ultimately penetrate into the abdominal cavity and affect adjacent organs. Metastases into the remote organs are rare. Recurrences at other parts of the scrotal sac after local removal of the first growth are evidently frequent, especially if hazardous work is continued. Second primary tumors may appear many years after the cessation of the exposure to soot (Curling [after 22 years]; Cooper). There are three cases on record (Paget; Lawson) in which

cancerous tissue seemed to have been present in the inguinal glands only, while the scrotal lesions were said to have regressed spontaneously (Butlin). These reports, however, are unreliable, as no microscopic examinations of the scrotal skin and of the lymph nodes were made (Bang). While Spencer claimed to have demonstrated soot particles in the inguinal nodes and contended that these chemical agents elicited primary neoplasia in these organs, there exists no evidence that exposure to soot caused at any time the development of malignant lymphomas. The histologic examination of the cancerous lesions in the skin of chimney sweeps showed in every case the presence of cornified squamous cell carcinomatous structures, exhibiting a low degree of proliferative activity.

VII. PREDISPOSING FACTORS

Among the various predisposing factors of general nature which have been considered in connection with the development of soot cancer, the changes attributed to physiological tissue senescence have played an important role. Considering the fact that soot cancer has a preparatory period of 15 to 25 years (Ullmann; Epstein), and relating this observation to the factors which caused the shift in the manifestation age of chimney-sweeps' cancer mentioned previously, there exists no sound reason for postulating such an age predisposition. Bang noted, on the other hand, that there occur apparently individual differences in the carcinogenic reactivity to soot, which may be possibly responsible in part for the development of chimney-sweeps' cancer in children following a relatively short occupational exposure to soot (Kennaway). Whereas the marked discrepancies in the geographic distribution of this type of industrial cancer might suggest the existence of racial differences in susceptibility, the available evidence militates against such an explanation (Bang).

More serious consideration is deserved, on the other hand, for the possibility of a familial sensitivity to the carcinogenic action of soot. Claims to this effect are based on the repeated observation of several cases of soot cancer in the same family. Earle recorded the occurrence of scrotal cancer in four members of one family of which three generations were sweeps. Crow reported the presence of a scrotal cancer in father and son, both chimney-sweeps. In this family there were eight deaths from cancer [four of them in chimney sweeps (2 on cheek, 1 on hand, 1 on scrotum)]. Cusack, Hawkins, and Paget noted the occurrence of sweep's cancer in several members of one family. White mentioned that soot cancer was formerly so frequent in certain types of occupations and districts that it was recognized as a family complaint.

It is, however, very doubtful whether this cumulation of cancer in soot-exposed families can be considered justly as an indication of a special genetically conditioned hypersensitivity, as there existed under such circumstances not only an occupational exposure to soot, but usually also an environmental

one, because the individuals employed as sweeps carried the soot home with their clothes, as well as in bags for storage and later disposal, providing thereby a very early, intimate, intense and prolonged contact of the entire family with this agent. It is moreover not readily conceivable that there should exist a genetically transmissible susceptibility of the scrotal skin to cancer, particularly as this organ exhibits an equally high liability to malignancy in several other occupations (mule spinners, tar workers, and pitch workers), where there is no question of a hereditary, but only of an acquired exogenous factor.

The predominant location of the soot cancer in the scrotal skin indicates the existence of locally predisposing factors, which are of similar nature to those producing the scrotal pitch cancer. In addition to factors of mechanical character (friction of the clothing, trauma from coarse particles), thermic trauma and the macerating influence of sweat which may facilitate the penetration of the carcinogenic agents contained in the soot through the epidermis, the anatomical structure of the scrotal skin plays apparently the principal role in this respect (Carozzi). The rugosities of the skin that favor the retention of soot and the large and numerous sebaceous glands that facilitate the penetration of the soot are the chief predisposing factors (Bang; Roussy and Héraux; Leitch; Bell). It must be pointed out, however, that this scrotal predisposition is operative only under the conditions of exposure prevailing in chimney sweeps, as the most frequent sites of cancer in soot workers of other occupations [employees of lamp black factories (Hope), stokers of coke ovens (Ullmann), gardeners (Earle)] are on those parts most exposed, that is, the fingers, hands, face, and feet.

VIII. EXPERIMENTAL SOOT CANCER OF THE SKIN

The first attempts Leitch made to produce experimental soot cancer of the skin failed. These negative results were obtained when soot was rubbed into the scrotal skin of rabbits and rats, and when mice were kept for a period of several months in boxes containing soot for bedding. Leitch prepared a solution of soot in sebum, which, after filtration, was a dark brown fluid. This material was applied to the skin of mice and the scrotum of rabbits. Two rabbits developed scrotal warts, which however, did not recur after the animals bit them off. A wart in a third rabbit showed progressive growth. Three of the mice treated with the soot solution developed papillomas, the earliest of which appeared after 35 days of painting. Two epitheliomata were present after 9 and 16 months, respectively.

Similarly successful experiments with soot were reported by Passey. This investigator used ordinary household soot, from which he prepared three fractions. The first fraction was a simple ether extract which after filtration was evaporated to a syrupy consistency. The second fraction was prepared by mixing 3 parts of soot plus 1 part of quick-lime with water into a thick

paste, which, after drying and removal of the abundantly formed ammonia, was broken up and then extracted with ether. The extract was distilled and evaporated to the consistency of syrup. The third fraction was composed of 1 part of the second fraction to which was added 10 parts of n/10 HCl. The mixture was shaken in a separatory funnel and the watery fraction was removed. This procedure was repeated until the watery solution running off was colorless. The collected watery solution was then made alkaline with caustic soda until yellowish droplets of oil appeared in the fluid, which was extracted with ether. The ether extract in turn was distilled and evaporated to a syrupy mass. White mice were painted with these three fractions. Warts were obtained in mice treated with the first and third fractions after 6 months of painting. Sixteen of eighteen surviving mice treated with the second fraction showed after 31 applications given within 10 weeks warts, of which 50 per cent were malignant after 3 months of this treatment. The active portion present in the second fraction was found to be contained in the material which distilled over at 250°C.

IX. PRECAUTIONARY MEASURES

Chimneys should be constructed or rebuilt in such a way that they are straight ducts which can be cleaned from above or from below without being entered. The cleaning should be done with a root broom. The removal of the loosened soot is done most effectively with specially constructed vacuum cleaners, which are widely used in the United States. Sweeps should wear special protective clothing fitting snugly around the neck, wrists and ankles, but loosely in the crutch. The sweep should be obliged to take a full bath every day and scrub with soap and water. His working clothes should be laundered at least once a week. The soiled clothes as well as the soot should not be brought into the living quarters. Where open fire-places are continuously used, care should be taken that they have sufficient draft so that the fuel is effectively burned and as little soot formed as possible. The use of coal suspected of producing a carcinogenic soot, such as apparently mined and burned in England, should be discouraged whenever possible. Medical inspections in intervals of six months should be made obligatory for chimney-sweeps.

X. MEDICO-LEGAL ASPECTS

Cancer of the skin caused by occupational exposure to soot is recognized as a compensable industrial neoplastic disease in Germany, Russia, Bohemia and Ohio. Such lesions are covered by laws in other countries by being included among the skin ulcers and epitheliomata produced by tar and its derivatives.

The first laws regulating the activities of chimney-sweeps with consideration of scrotal lesions were passed in England in 1788, when it was decreed by

an act of Parliament that an apprenticeship in this profession should not start before the age of 8 years. Prior to that time, boys as young as four years had been accepted as climbing boys. It was prohibited that any one master-sweep employed more than six apprentices. To curb further the existing excesses of industrial exploitation and to insure a more adequate care and supervision of these youngsters, it was required that they should be kept clean and should be given a bath at least once a week (Oliver). The age limit for apprenticeship was raised to 10 years in 1834 and the number of apprentices for any one master-sweep was restricted to four. The age limit was again extended in 1842 to 16 years. It was decreed at the same time that climbing-sweeps should be at least 21 years old. Twenty years later it was made illegal for master-sweeps to employ boys less than 10 years of age in any other work and only within the place of business and in the yard.

It is obvious that all these laws were neither obeyed nor enforced. This fact is clearly demonstrated by the way in which the census of sweeps in England was conducted until rather recent years. The official sweep census figures of occupied males included originally all sweeps of 10 years and over. This procedure was not changed until 1912, when the age limit was raised to 12 years and over, while it is 14 years and over since 1931. The census taken in 1811 showed that there were still 99 sweeps between the age of 10 and 14, and 611 sweeps between the age of 15 to 19. There were 1,852 sweeps under 20 years of age in 1841; in 1851, 183 sweeps between 5 to 9 years, 924 sweeps between the age 10 to 14 years, and 2,045 sweeps below 20 years of age. A minor improvement to this distressing situation had taken place when the census was taken in 1861. At that time there were 67 sweeps 5 to 9 years old; 569 sweeps 10 to 14 years old; and 1,503 sweeps below the age of 20. In 1871 five boys from 5 to 9 years of age were still listed as sweeps; 243 were from 10 to 14 years old; and 1,054 were below the age of 20. In 1921 there were only 203 below the age of 20; while in 1931 the number of sweeps below 21 years of age had dropped to 198 (Henry).

SOOT

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g. Aromatic Hydrocarbons, Coal Tar Dyes, Intermediates and Related Substances

The numerous aromatic derivatives of the fractionation of tar and petroleum, especially the cyclic nitro- and amido compounds (dye intermediates) as well as many finished products, such as coal tar dyes, represent an important and frequent source of occupational and non-occupational dermatitis and dermatosis, as these products come in contact not only with handlers of these substances in chemical plants and their users in other industrial establishments (textile industry, rubber industry, electrical appliance industry, foodstuff

industry, pharmaceutical and cosmetic industry), but also with the multitude of consumers of the various types of merchandise into which these aromatic compounds are incorporated in a more or less loose and active form (White; Fuss; Eisner; Koelsch; Bering and Zitzke; Mayer; Schwartz; Sachs, Oppenheim; O'Donovan; and many others).

Inasmuch as occupational dermatoses from these and other sources form a high percentage of all industrial cutaneous diseases (80 per cent, Halikin) as well as of all occupational disorders (60 per cent, Eller and Schwartz), and in view of the fact that some of the aromatic compounds, being the cause of many of these skin manifestations, have demonstrated their carcinogenic properties by eliciting cancers of some internal organs, or are under suspicion of having such qualities, a discussion of the various aspects of industrial dermatoses originating from aromatic compounds in their relation to occupational cancer of the skin follows.

I. CHEMICAL AND TECHNOLOGICAL ASPECTS

It is obvious that the incidence of industrial dermatoses resulting from contact with aromatic derivatives of tar depends in any particular country to an extent upon the size and character of its industrial establishments and especially on the presence of plants engaged in the large scale production of organic chemicals. A large scale manufacturing of chemicals is carried on in the United States, England, France, Germany, Switzerland and Japan; a well developed, but less extensive chemical industry exists in Russia, Belgium, Canada, Netherlands, and Poland; small scale establishments are found in Bulgaria, Greece, Hungary and Rumania; while very little industrial chemical production is found in Argentina and Brazil. Only a small portion of the coal tar intermediates (refined naphthalenes, phenols, benzol, toluol, xylol, anthracene) are used for the manufacture of synthetic dyes. The greater part of the naphthalenes goes into the production of glycerol phthalates and carbon black. The phthalates in turn serve as a basic material for resins. Anthracenes with their accompanying carbazols and phenanthrenes are utilized chemically to a limited extent (the bulk of these are left in the pitch or heavy oil) for fuel or as a preservative of wood. Phenol is employed to a restricted degree in making dyes, but is mainly used for the production of disinfectants, synthetic resins, explosives, plastics, medicinals, flavoring agents and perfume materials. Other aromatic coal tar derivatives are represented by chemicals finding widespread application in the rubber industry as accelerators and catalyzers; in photographic trades, as developers and for other purposes.

II. EXPOSURE, INCIDENCE AND CAUSATIVE CHEMICALS OF DERMATOSES

The lists of occupations exposed to aromatic compounds causing dermatosis, as prepared by Dublin and Vane as well as Schwartz and Tulipan, convey an

appropriate picture of the vast extent of the industrial exposure existing in this respect: acetanilid workers, aniline makers, artificial-leather makers, calico printers, camphor makers, coal-tar workers, compositors, compounders (rubber), dye makers, dyers, explosive workers, feather workers, germicide makers, lithographers, millinery workers, mixers (rubber), nitroaniline workers, painters, paint makers, pencil (colored) makers, perfume makers, photographic-trade workers, pressroom workers (rubber), printers, reclaimers (rubber), tannery workers, varnishers, varnish makers, vulcanizers. To this list the following occupations must be added: shoe dyers, ink makers, soap makers, floor-polish manufacturers, pharmaceutical and industrial chemists, cosmetic workers, workers employed in food industry using dyes for coloring foodstuffs (citrus fruit, candy, preserves), textile workers, garment makers, furriers, fur dyers, handlers and manufacturers of certain insecticides, leather and shoe workers, and manufacturers of colored rubber goods.

The incidence of dermatoses among the workers of these different industries varies greatly as it depends upon the character of the chemicals handled and the operating methods employed. Foerster noted that in general the newer the industry and the newer the chemical compounds used, the greater is the number of cases of dermatitis, because of unknown and unfamiliar hazards, lack of protective measures, and lack of adaptation on the part of the employees to the work. Koelsch stated that Grandhomme, the factory physician of the leading dye industry in Germany, found that in 1883 to 1893 aniline workers showed the highest incidence of eczema (34.7 per cent), while alizarin workers came next with a frequency of 15.8 per cent. Similar numerical relations were observed by Leymann for the years 1899 to 1906 among the workers of a chemical plant using tar substances. The position which aniline workers occupied in this respect seems to have been retained, according to recent investigations of R. Fischer, cited by Koelsch.

Bachfeld reported the following incidence figures on dermatitis among workers in aniline intermediates in 1909 to 1914: among 100 intermediate workers per year, 4.5 cases; for the 6 years' period, 27 cases; among 100 dye workers per year, 7.66 cases; for the six years' period, 46 cases; among 100 finished dye workers per year, 1.16 cases; for the six years' period, 7 cases. The relatively low incidence of occupational dermatoses among the dye workers in more recent years is attributed by Koelsch to the usually innocuous character of the finished dyes to the skin. Dyes produced during the early period of the coal tar dye industry contained, on the other hand, many irritative impurities of organic and inorganic nature (arsenic, chromium), which gave rise to skin manifestations. Recent investigations, conducted by Schwartz on approximately 18,000 active employees of the rubber industries, oil refineries, dyeing establishments and candy factories in the United States, yielded 235 cases of occupational dermatoses. Schwartz estimated that more than one per cent of the workers engaged in basic industries are affected

annually by dermatoses. The same investigator found chemical burns and dermatitis in 16 per cent of the 2,500 workers employed in a dyeing establishment, while the frequency of such cutaneous lesions was as high as 50 per cent among the workers of a plant in which synthetic waxes and resins were handled. In an analysis of 9,116 cases of occupational dermatoses reported to the United States Public Health Service, Schwartz noted that 4.3 per cent of the cases had occupational contact with dyes and dye intermediates (exclusive of fur dyes); 2.8 per cent were exposed to rubber and its compounds; 1.1 per cent handled furs and fur dyes; 1.1 per cent were exposed to miscellaneous coal tar products, making a total of 8.3 per cent (843 cases) of the total number of industrial dermatoses possibly caused by contact with aromatic compounds. Regarding the frequency of such reactions among skin diseases in general, Ingram observed that there were 30 cases of dye dermatitis (12 from the use of hair dyes, 7 from contact with fur dyes, 11 by exposure to fabric dyes) among 12,000 cases of skin diseases of various types.

Among the various dyes which may act as skin irritants or sensitizers, the ursol dyes (para- and meta-phenylenediamine and derivatives) that are used extensively in dyeing furs, are most prominent, because a congenital hypersensitivity against these substances is relatively common (Mayer). Downing stated that one out of 100 individuals is allergic against ursol dyes, while Ingram found through patch tests performed routinely on 1,000 patients that even 4 per cent of the examined persons showed positive reactions to these compounds. Because of this fact various associations of cosmetic manufactures decided to refuse membership to firms using ursol compounds in hair dyes (Downing). A relatively frequent source of dye dermatitis has been dyed leather, particularly the straps of wrist watches, dyed with oil yellow T (amido-azotoluene hydrochloride) (Schwartz), while the chemically closely related aniline dyes, oil yellow OB (orthotoluene-azo-beta-naphthylamine), oil yellow AB (benzene-azo-beta-naphthylamine), and ortho-toluene-azo-beta-naphthol, which have been employed extensively during recent years to color Florida oranges, have not given rise to a high incidence of dermatitis, according to the information available (Traub, Gordon and Van Dyke; Schwartz). There exists a limited number of cases of dye dermatitis among handlers and consumers of numerous dyed articles such as fabrics, furs, shoes, hosiery, foodstuffs, skin creams, nail dyes, eye brow pencils, lipsticks, and rouges which were caused by a congenital or acquired hypersensitivity to the particular dyes or groups of dyes and which resulted from a cutaneous or alimentary contact with these substances (Simon and Rackemann; Bonnevie and Genner; Blumenthal and Jaffé; Baer; Schwartz; Criep; Mackenna; Bloch; Lewis; Stauffer; Grasreiner; Anderson and Ayres; Lanzenberg; Beerman; Ingram; Niles; Ramond and others).

Schwartz noted that all nitro- and nitroso-compounds used in the dye industry are skin irritants and sensitizers to a considerable percentage of individuals. Dermatitis has resulted from the occupational contact with numerous dye intermediates and dyes, such as benzidine, alpha- and beta-naphthylamine, benzanthrone, anthraquinone, aniline, aminoazobenzol, toluidine, aminophenol, cresol, benzoyl paraamino-benzol, aniline black, bismarck brown, orange Y and R, aniline blue, methyl violet, aniline yellow, aurantia, butter yellow, chrysoidin, benzidine fuchsin, water blue, brilliant green, malachite green, eosin, scarlet red, brilliant congo, trypan red, brilliant black, naphthol yellow, metatoluene diamine, metaphenylene diamine, paraaminophenol, paraphenylenediamine, aminoazotoluene, oil red N-1700, oil orange 7-78, orange I, hexanitrophenylamine, etc. (Bering and Zitzke, Schwartz; and others). The eczematoid action exerted by these compounds is facilitated by the presence of abrasions, perspiration (Wieder; Schwartz; Sachs). The irritative action upon the skin is occasionally brought out when the dyes are decomposed. Schwartz and Hocker reported the occurrence of dermatitis among splicers of telephone cables in which the conductor insulation was colored with green and blue dyes, which became irritants only when the cable insulation was boiled in splicing oil. The irritative effect of colored material is elicited in other instances not by the dye itself but by irritative dye intermediates present as impurities in the dye or used as solvents, such as for instance in shoe dyes (nitrobenzol, orthochlorobenzene, aniline, orthotoluidine).

Some of the dyes, dye intermediates, as well as other aromatic substances displaying eczematoid properties, are employed in other industries and give rise to cutaneous eruptions among their workers. Accelerators used in the rubber industry (mercapto-benzo-thiazole, butyraldehyde aniline, condensation products of aniline and aldehyde, thiocarbanilide, para-nitroso-dimethyl aniline), anti-oxidants (phenyl-beta-naphthylamine, phenyl-meta-naphthylamine, paraphenylene diamine, di-tolylamine, metatoluylene diamine, phenyl-alpha-naphthylamine), as well as coloring matter (lamp black, dyes) represent skin hazards of this type (Schwartz). Finishes of socks (sulpho-resorcinol) and other aromatic, industrially used chemicals, such as phenylhydrazin and related hydrazins, fall into this category (Wright and Joyner; Hueper; Lewin; Schwartz; and others).

Attention is called to the fact that some of these substances do not have a direct irritative action, but exert a photodynamic effect (alizarin dyes, acridine, carbazols, eosin, benzanthrone, acriflavine, sulfanilamide, erythrosin, fluorescein, rose-bengal (Wieder; Brusting; Neuman and Sharlit; Haxthausen; Jodlbauer and Busch; Hellier) which results in the production of an actinic dermatitis and melanosis or leukoderma (Sandler). Vitiligo, on the other hand, following the contact with hydroquinone bodies is not the result

of a photodynamic action, but is caused by the antioxidant effect of these chemicals, which are incorporated sometimes in rubber goods (gloves) (Oliver, Schwartz and Warren; Oettel), upon the melanin metabolism.

III. CARCINOGENIC RELATIONS

The occupational exposure of the skin to aromatic compounds presents a number of different aspects regarding the production and course of cancer of the skin and of the internal organs which are doubtlessly of great importance, but in many respects are little understood.

The chemical relation of many of these substances with compounds of known carcinogenic properties as well as with the non-neoplastic dermatitis, and the dermatotic and pigmentary disturbances they produce suggests the possibility that carcinogenic sequelae may ensue in the skin on the basis of a chemo-specific, chemo-allergic or chronic irritative, non-specific basis. In addition to such primary and initiating carcinogenic action, they may play a contributory role in the causation of solar cancers of the skin because of the photodynamic activity some of them exhibit. Moreover there exists the possibility that they may influence the development and course of other cutaneous malignancies of known or unknown etiology. Inasmuch as the aromatic compounds, which elicit cutaneous reactions, as well as others apparently innocuous to the skin, are resorbed into the body, the skin may represent the organ of entrance for substances, either directly or in a metabolized form, producing malignant tumors of internal organs (urogenous tract, alimentary tract).

The evidence indicating the existence of a direct carcinogenic effect of these aromatic substances upon the skin is of scanty and doubtful value. Hoffman noted that tailors and textile workers show an excessive incidence of cancer because of their occupational contact with dyes fixed in the fabrics they handled. Mishell stated that workers in aniline dye plants often develop sores on the exposed parts of the skin, which in time may become malignant. Haagensen recorded three cases of skin cancer found in individuals occupationally exposed to dyes (packer of dyed cloth with cancer of the lip; dyer with cancer of the eyelid; shipper in a dye factory with basal cell cancer of the back of the hand, keratoses on hands and face and chronic dermatitis), but he did not believe that these neoplasms were caused by these substances. Finally, Sharlit reported the development of a melanoma on the forehead at the site of a stab with a pencil of indelible ink (methyl violet) 6 years previously. Inasmuch as histological diagnoses made by several pathologists of the tissue removed differed between inflammatory melanotic lesion, benign melanoma, and malignant melanoma, and, in view that there was no recurrence and there were keratoses of the palms and soles present, it appears probable that the resulting lesion was not of neoplastic nature. Koelsch mentioned the appearance of cutaneous papillomata in a lithographer, 19 years

old, following an occupational contact with aniline dyes, but stated that these manifestations were apparently due to the existence of an individual predisposition. Baló and Korpâssy cited Walker and Oppenheim concerning the occurrence of papillomatous warts in tattooed skin.

The attempts of an experimental production of cutaneous cancers by the external or subcutaneous application of coal tar dyes and their intermediates were essentially unsuccessful. Following the production of atypical and carcinoma-like epithelial proliferations in the ears of rabbits by the subcutaneous injection of scarlet red by Fischer-Wasels, a large number of investigators tried, with negative results, to elicit progressive and truly malignant growths by the introduction of this and other dye derivatives of aminoazotoluol and aminoazobenzol as well as similar aromatic amino-compounds (sudan III, scarlet red, aniline, benzidine, toluidine, naphthylamine, indol, skatol, etc.) (Stoeber and Wacker; Schmieden and Hayward; Stoeber; Hayward; Martinotti; Lüth; Yamauchi; Eckert, Cooper and Seelig; Helmholz; Jores; Stahr; Meyer; Wessely; Zacharjewskaja; Waelsch; Schreiber and Wengler; Sachs; Kern; Henkel; Butlin; Rutschinsky; Mayer; and others).

While the experiments demonstrated clearly that the aminoazotoluol and aminoazobenzol derivatives exerted a definite and marked epithelial proliferation stimulating effect, any epithelioma-like lesions thus produced regressed spontaneously as soon as the exposure to these dyes ceased. Sachs obtained a verrucous thickening of the skin of rabbits, when the following dyes were rubbed into the skin: scarlet red, brilliant green, yellow light, and acid yellow. The lesions obtained exhibited a proliferation of the sebaceous glands; atypical epithelial pegs extended from the basal layer. Martinotti, who investigated the epithelial growth stimulating action of a series of aminoazobenzol derivatives, found that the effect is maximal with the lower members of this series and decreases with the higher compounds. An increased activity, however, was displayed by the diazo- and triazo-compounds. Among the finished dyes tested, chrysoidin exhibited the most marked epithelial proliferation stimulating effect. Shear recently succeeded in producing cancers of the skin in small rodents by the subcutaneous injection of aromatic amines and azo-compounds.

Inasmuch as some of these substances (aromatic amines, aminoazotoluol derivatives) are the cause of occupational cancer of the urogenous tract or of experimental cancer of the alimentary tract, respectively, these reasons have been advanced to explain the negative results seen. It has been maintained that these compounds are very rapidly resorbed from the site of cutaneous introduction, so that the exposure of the skin to these substances is not sufficiently long and intense for eliciting a carcinogenic epidermal response, while the conditions prevailing in these respects in the internal organs affected favor carcinogenesis (Martinotti; Brock, Druckery and Hamperl).

Little consideration has been given so far to the possible contributory role

which an occupational contact with photodynamic dyes may exert on the production of solar cancer of the skin. Experiments of Büngeler and Roffo have demonstrated in animal experiments that the application of photosensitizing dyes accentuates the carcinogenic action of the ultraviolet rays.

It is a well established fact that many of the dermatoses following the industrial contact with dyes and related compounds develop on the basis of a chemo-allergy, caused probably by the intracellular formation of allergens by a combination of protein complexes with quinonic conversion products of the dyes (Mayer; Suida; Gerdon), but little definite evidence exists that these chemo-immune reactions play a role in any of the scanty neoplastic reactions observed. Cannon, however, reported the appearance of lymphoblastoma-like lesions of an allergic nature in the skin of persons exposed to hair dyes, furniture paints, and similar materials.

The apparent rarity of epitheliomatous responses in the skin of individuals affected by chronic dermatitis and dermatoses of chemical origin (aromatic compounds as well as other chemicals, such as formalin, solvents, thinners, alkalis, acids, cement) strongly indicates that chronic, nonspecific chemical irritation does not play any important role in the causation of skin cancer.

There are *no clinical experiences* on record concerning an influence of an occupational exposure to dyes and related compounds upon the course of a malignant tumor located in a remote organ. This question has been investigated, however, in a large series of *experiments* (Werner; Forssman; Roffo; Marsh and Simpson; Simpson and Marsh). Werner saw a growth-stimulating effect by scarlet red upon a spontaneous mouse-cancer when this dye dissolved in olive oil was introduced in places remote from the site of the neoplasm. Forssman injected a large number of dyes intraperitoneally into mice which were painted simultaneously with tar. Of the numerous dyes used (basic and acid azo dyes, benzidine dyes, triphenyl-methane dyes, phthalein dyes, pyronin dyes, oxazine dyes, thiazine dyes, azine dyes), none seemed to have any effect, favorable or unfavorable, upon the development or incidence of tar tumors. Marsh and Simpson employed in their experiment a total of 145 different dyes which they injected intravenously into mice with spontaneous mammary cancers. While none of the dyes exerted any favorable therapeutic effects, several seemed to stimulate the growth of the mammary carcinomas (naphthol yellow, acid fuchsin, gentian violet, diazine green, rhodamine, toluidine blue, and others). In view of the varying histological character of the spontaneous breast cancers in mice and considering the normal variations in growth rate of these tumors with their periods of regression because of the frequent occurrence of extensive intratumoral necroses, it seems to be doubtful whether the observations made can be considered as significant.

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h. Chemical Traumatic Carcinomas of the Skin

A number of chemically diverse substances, usually exerting a marked necrotizing and caustic effect (chemical burn) upon the exposed tissue, have been incriminated occasionally in the production of accidental cutaneous cancers, and these generally arose as the result of a single, acute injury. Bland-Sutton recorded a case of epithelioma of the arm developing from an ulcer caused by a caustic soda burn. Andrews and McNitt noted the development of palmar keratoses following sulfuric acid burns. One of the earliest reports of cutaneous malignancy arising on the basis of a scar stated that a burn caused by sulfuric acid was responsible for the cicatrization [Dupuytren (1839)]. A similar case, recorded by Mishell, reported a carcinoma of the hand in a dye worker, who had sustained, six months previously, a burn from a splash of sulfuric acid. The ulcer initially formed never healed completely, but grew noticeably three months following the accident. It is doubtful whether a case of cancer of the eyelid, developing four weeks after a crude carbolic acid burn was sustained, belongs to this group of cancers from chemical burns, as crude phenol contains tarry impurities, thus making it more likely that this case belongs to the acute tar carcinomas (Story). Gougerot, Burnier and Eliascheff observed the occurrence of a transitional basal cell cancer in the nose of a woman, 40 years old and employed in a rubber factory, which appeared one year after an accidental burn by hot carbon disulfide.

While the investigators reporting this case expressed the opinion that the thermic trauma played the main role in bringing about the neoplastic sequela by facilitating the penetration of the carbon disulfide through the skin, recent studies of Hueper showed that carbon disulfide can produce a burn, if its rapid evaporation is interfered with, and that hyperplastic epithelial proliferation may appear in the edges of the resulting ulcers. On the other hand, it appears probable that an epitheliomatous ulcer, found about 90 days after a burn of the cheek produced by the burning phosphorus head of a match, is not the result of a chemical burn but is related to the thermic trauma (Gaté). Considering the frequent occurrence of chemical burns in chemical workers (organic and inorganic acids, alkalis, solvents, etc.), these isolated cases of carcinoma of the skin following chemical burns suggest strongly that they are exceptional sequelae of such injuries and, apparently, result only when more important additional causal factors are active. This conclusion is supported by the fact that there exists one single and unconfirmed observation concerning the successful experimental production of cutaneous cancers in mice by the prolonged application of hydrochloric acid and potassium hydroxide (Narat).

Finally, mention may be made in this connection of a statement of Ross who commented on the high frequency of cancers on the hands and arms in farmers who handle manure. This observation possesses a certain relation to

a report of Mishell on the excessive incidence of cutaneous malignancy among guano workers, an observation, originally recorded by Richer and subsequently cited by Green and continued to be quoted in the literature without further verification.

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3. PHYSICAL AGENTS

A. ACTINIC AGENTS

a. SOLAR AND ULTRAVIOLET RAYS—I. PHYSICAL AND TECHNOLOGICAL ASPECTS

Solar rays consist of non-corpuscular electro-magnetic waves of varying wave-lengths. Depending upon their wave-lengths, these elicit in part in the human eye sensations of different colors. In addition to the *visible part* of the solar spectrum, extending between rays of 7,000 ångstrom units (red) to 4,000 ångstrom units (violet), there exist *invisible parts* on both sides of this zone, that is, the infrared and ultraviolet rays.

The infra-red part of the solar spectrum contains rays of from 7,000 to 8,000 ångstrom units, while its ultraviolet portion is composed of rays of from 4,000 to 2,000 ångstrom units.

Still shorter ultraviolet rays emitted by the sun are absorbed in the atmosphere before they reach the surface of the earth.

Apart from this natural source of visible and invisible solar rays, several artificial rays used in medical therapeutics as well as for certain industrial purposes exist. Mercury vapor lamps produce mainly ultraviolet rays, while carbon or metal arc lamps emit in addition to these rays varying amounts of visible and infrared rays, depending upon the type of carbons used. The ultraviolet rays emitted from these sources are shorter than those obtained from the sun, being as short as 1,500 Å.U. With a progressive shortening

of the wave length of the ultraviolet rays, they approach gradually soft roentgen-rays, whereas, with a further lengthening of the wave-length of the infrared rays, the region of the short radio-waves is reached. It is characteristic for the electro-magnetic waves composing the solar spectrum that their penetrability increases with their wave-lengths, in contrast to the electro-magnetic waves representing roentgen-rays and gamma rays which exhibit an opposite relation between penetrability and wave-length (Hausmann and Haxthausen; Laurens; Pincussen).

II. EXPOSURE

Apart from the normal environmental exposure to solar rays which may be especially marked in individuals given to the habit of sun-bathing and outdoor sports, there occurs a more or less extensive contact with these actinic agents in all persons having outdoor activities (farmers, herders, sailors, road-workers, construction workers, drivers of vehicles, fishermen, railroad workers, gardeners, lumbermen, vine growers, etc). An abnormal degree of industrial exposure to ultraviolet rays from artificial sources may exist for attendants in actinic therapy departments and in industrial establishments in which artificial ultraviolet rays are used for the production of photochemical reactions (vitamin D manufacture, pasteurization) or in which these rays are incidental by-products (arc welding). It is obvious that the degree of exposure to solar rays and especially, to their ultraviolet portion depends greatly upon the climatic and other environmental conditions, which affect the intensity of radiation (surface of water, snow, sand). The inhabitants of regions in which a dry and sunny climate prevails and in which warm weather permits prolonged occupational activity outdoors and necessitates a relative scantiness of clothing are markedly and extensively exposed to solar rays. It is evident that in the statistical evaluation of differences of biological effects from excessive solar irradiation in various regions, these factors must be taken into proper consideration. The use of mean temperatures for such purposes is apt to lead to incorrect conclusions, as such figures do not reflect sufficiently the intensity and duration of solar radiation actually effective.

III. GEOGRAPHICAL AND OCCUPATIONAL DISTRIBUTION AND INCIDENCE

Ramazzini (1633-1714) was the first to note the occurrence of a rough keratotic skin in fishermen. However, it was Unna who recognized first (1894) the interrelation between an excessive exposure to solar rays and the production of cancer of the skin, when he described the sailor's skin as a precancerous condition, which he attributed to the prolonged and severe occupational exposure of sailors to strong solar irradiation, wind and weather. Unna suggested that the ultraviolet rays contained in the solar radiation play a major causal role in the development of the cutaneous responses observed. A similar etiological mechanism was claimed by Kyrle to be operative in the

production of the precancerous lesions (keratosis senilis) found on the exposed parts of the skin during advanced age. This investigator also called attention to the great similarity existing between the cutaneous pigmentary and hyperkeratotic manifestations found in sailors and old individuals and the cutaneous changes observed in children suffering from xeroderma pigmentosum caused by a congenital hypersensitivity to solar rays, and resulting ultimately in the appearance of multiple carcinomas of the skin. Kyrle called the cancerous dermatosis, as seen in sailors, the xeroderma pigmentosum of the adults, representing the neoplastic end result of a cutaneous cancerous predisposition acquired by a prolonged and intense exposure to sun rays. Pusey advanced a similar conception when he noted that an excessive exposure to actinic energy produced an exaggerated picture of senile skin, which he considered to be caused, largely, by a less powerful action of solar rays exerted over a long period of years.

These observations made in sailors were extended later to members of outdoor occupations such as farmers and agricultural laborers (Dubreuilh; Lawrence; Hyde; Crawford; Molesworth; Larabi; Roffo; Peller and Stephenson; Haagensen; Findlay; Laurens; Dalons and Constantin; Sutton; Gasquet; White; Phillips; and others).

Hyde (1906) mentioned that in the sunny and dry regions of the Middlewest (United States) deaths from cancer of the skin were found mainly in males with outdoor occupations (farmers, boatmen, gardeners, nurserymen, vine growers, lumbermen, pilots, fishermen, steam railway employees, sailors). Agricultural laborers constituted nine-tenths of this group.

Sutton (1915) emphasized the fact that long continued exposure to strong sunlight plays an important part in the production of seborrhoeic keratoses or sailor's skin. This investigator noted that this skin condition was probably more common among the inhabitants of the sunny plains of Kansas than among those living in Newfoundland. Among 31 cases of skin cancer, Sutton observed, 16 were exposed to solar-rays to a high degree (farmers, stockmen, cattle men, oil operators, ranchmen, engineers, house painters, rural mail carriers, street car conductors). In a recent study of the histories of more than 1,000 cases of cutaneous malignancy observed during the years 1913 to 1938, Phillips found a particularly high incidence of these lesions situated on the exposed parts of the skin among persons with outdoor occupations who lived in the sunny climate of Texas, Oklahoma and New Mexico. Phillips concluded that there exists a causal interrelation between these conditions.

Similar relationships were reported by Apperly to exist for the inhabitants of those parts of the United States in which a relatively high mean temperature (above 42° Fahrenheit), and thus a rather intense solar radiation, prevailed. Peller and Stephenson, who analyzed the incidence of skin cancer among the personnel of the United States Navy, observed that epitheliomas occurred eight times as frequently as among the civilian population. The

intense and prolonged exposure to direct and reflected solar rays was considered to be responsible for this phenomenon. In a recent statistical study on the geographical distribution of cancer in the United States, Mountin and Dorn noted that skin cancers claim proportionally more victims, both male and female, among the white population in the South as compared with the remainder of the country, but that among other regions the difference is of little moment. These investigators are uncertain whether these variations can be attributed to a greater exposure of the inhabitants of the Southern States to solar radiation, as many of the Western States with a very hot summer season and relatively more clear weather throughout the year, report the lowest mortality from skin cancer.

In view that cutaneous cancers are, in general, not only the least malignant biologically as well as the most easily diagnosed and, therefore, most readily cured, the mortality rate from skin cancer depends to some extent upon the type and the degree of medical care that exists in a particular region. Therefore, differences in mortality rates of skin cancer may not always reflect reliable morbidity rates if marked discrepancies in the medical care of various localities exist. Moreover, it may be pointed out that the Western and Southern States are not comparable in climate because of the marked differences in altitude existing between these two regions, which will favor the use of protective clothing in the higher and therefore colder regions during the larger part of the year. Murray pointed out that the considerably lower incidence of cutaneous cancer in southern California with its bright sunlight may be due to a comparative lack of exposure of the white population there to the sunlight, as the rural outdoor work in this part of the country is done almost exclusively by the more markedly pigmented Oriental or Mexican laborers, whose pigment protects them from the carcinogenic effects of solar rays. In the Southern States, on the other hand, a large proportion of the white population engages in outdoor field labor and the population is more exposed to sunlight, thus accounting for the greater prevalence of cutaneous cancer in these other Southern States.

Additional support for the existence of causal connections of this nature was supplied by Roffo from the South American continent (Argentina), who noted that extensive solar irradiation was evidently the etiological factor determining the site of skin cancer as 95 per cent of 1,500 skin cancers were located in the face and nose, 3.07 per cent affected the back of the hands, 0.52 per cent the dorsum of the feet, and only 1.02 percent were situated on the haired parts of the skin.

Similar observations were reported from the dry and sunny lands of Australia. Molesworth, as well as Lawrence, commented on the high incidence of keratoses and cutaneous cancers among the white population of Australia in comparison with the much lower incidence of such lesions among the racially related inhabitants of England, Scotland and Wales, as well as of the

United States, in parts of which, however, the frequency of skin cancer approaches that found in Australia because of similar climatic conditions. Lawrence recorded that 13.23 per cent of 20,000 patients suffering from dermatological diseases exhibited one or several of the three manifestations characteristic of solar dermatosis (4.38 per cent, keratoses; 6.82 per cent, rodent ulcer; 1.975 per cent, epithelioma). Paul stated that skin cancer was the most important cutaneous lesion in Australia and was caused by exposure to actinic energy. Duhig mentioned that in Queensland, Australia, cancer of the skin was common in men and usually affected the face, ears, and back of hands, that is, the exposed parts of the skin.

Additional confirmatory evidence in this respect was supplied by Maisin who noted that the moderately deep pigmented Chinese and Malayan inhabitants of the Dutch East Indies who usually go bare-legged have often cancer of the foot, for the causation of which this investigator incriminated an extensive exposure to sun rays in combination with trauma and infection.

Observations made by Dubreuilh in southern France (Bordeaux) during the years 1890 to 1907 showed that precancerous lesions (senile keratoses) were especially frequent among old people coming from rural districts and were often associated with keratinizing epitheliomas even when occurring in younger outdoor workers. In view of the predominant location of these manifestations on the exposed portions of the skin (face, dorsal aspect of hands, less often forearms and neck) and because of their morphological similarity with the cutaneous changes found in xeroderma pigmentosum, Dubreuilh concluded that sun-light, and particularly its ultraviolet portion, was responsible for their production.

IV. EXPERIMENTAL SOLAR AND ULTRAVIOLET CANCER

The circumstantial clinical and statistical evidence suggesting a carcinogenic action of a prolonged and intensive solar irradiation upon the human skin is supported to some degree by the experimental results obtained in mice and rats which were exposed to solar and ultraviolet rays (Findlay; Putschar and Holtz; Roffo; Wahlgren; Rusch and Baumann; Knudson, Sturges and Ryan; Beard, Boggess and von Haam; Herlitz, Jundell and Wahlgren; Büngeler; Hueper). Findlay was the first investigator who produced cutaneous malignancy in albino mice with the aid of ultraviolet rays, while studying the hastening effect which this agent exerted upon the development of tar cancers. Out of nine mice surviving for more than 32 weeks a daily application of ultraviolet rays from a quartz lamp upon a depilated area of the skin, four animals developed carcinomas and three mice papillomas.

Putschar and Holtz, who used not only albino rats, but also beige and hooded rats, obtained carcinogenic responses in animals exposed to the rays emitted from a mercury arc lamp for periods which increased from 2 minutes daily at the start to 24 hours during the latter part of an experiment which

lasted for eleven months. Of 35 animals thus treated, seven showed local thickenings of the epidermis of the initially depilated area of the back, five had benign epithelial neoplasms (papillomas), four exhibited atypical, "regenerative" epithelial proliferations, six displayed epithelial lesions suspected of being malignant and thirteen possessed carcinomas.

It was noted that the majority of the neoplastic responses affected the ears and the regions around the eyes. Only an occasional tumor developed in the primarily depilated area of the back, which, however, became covered during the later stages of the experiment by a dense and abundant hair growth absorbing the larger portion of the actinic energy and thus interfering with its carcinogenic action.

Knudson, Sturges and Ryan obtained in white and piebald rats, irradiated from a distance of 4 feet for 20 hours daily, the first cancers involving mainly the nose, eyes and ears after 5 months from the start of the experiment. Similar results were reported by Herlitz, Jundell and Wahlgren who observed the formation of usually multiple cutaneous cancers in 17 mice surviving an exposure to ultraviolet rays for over 200 days. The neoplasms developed in those parts of the skin normally covered by a scanty hairy coat (ears, base of tail). Corresponding observations were made by Roffo, who exposed numerous rats to ultraviolet rays over prolonged periods and obtained epithelial neoplasms of the skin in similar locations (ears, back of head, region of eyes, nose, fore-feet). His results were confirmed by Beard, Boggess and von Haam, as well as by Rusch and Baumann, the first mentioned investigators using albino rats, while the last mentioned authors employed albino and black coated mice. Negative results with mice reported by Kohn-Speyer are attributable to the application of insufficient doses of ultraviolet rays. Hueper reported recently the production of cancers in albino, white, hooded and grey-black haired rats as well as, exceptionally, in congenitally hairless rats.

Similar neoplastic lesions of the skin were elicited in rats and mice by a prolonged exposure to strong solar irradiation (9 to 10 months) by Roffo, who reported a total of 140 tumors of the ear, 58 neoplasms of the eye region and 15 cancers affecting the feet. These results were substantiated by Roussy, Hartmann and Bèclere as well as Büngeler.

V. PREDISPOSING FACTORS

Sex. Several investigators commented upon the higher frequency of solar cancer of the skin among males than among females, and related this phenomenon, in part, to differences in the light sensitivity between the sexes, and in part, to exogenous factors causing a lesser exposure of women to sun rays. Laurens thus pointed out that men are in general 20 per cent more sensitive to solar rays than women. The reason for this discrepancy between the two sexes is not clear, inasmuch as the female skin is, in general, thinner than the skin of males. The pigment metabolism of the female skin, on the other

hand, is subjected more markedly to the influences of sex hormones as evidenced by the appearance of hyperpigmentations and pigmentary shifts during the menstrual period and particularly during pregnancy (chloasma uterinum). The lack of estrogens has been related, moreover, to the appearance of light hypersensitivity and dermatoses in women (Lancaster). Ellinger ascribed the higher sensitivity of the male skin to the presence of a denser capillary bed in the skin of man in comparison to women, who, however, show an increased number of capillaries during pregnancy. Roffo, on the other hand, asserted that the differences in the susceptibility of the two sexes to solar cancer (70.99% in men, 29.19% in women) were artificially conditioned, that is, that the lower incidence of solar cancer in women was caused by the use of powders and cremes applied by women in the care of their skin. Duhig argued that the almost complete absence of solar cancer of the neck in women was attributable to the protective action of long hairs and to the wearing of hats with wide brims by women. This investigator believed that such factors accounted in part for the fact that cutaneous malignancy in Australia was four times as common among men as women.

Race. Marked differences in the sensitivity of different races to solar rays exists. These variations are ascribable to several factors, such as degree and type of skin pigmentation, amount of cornification, oiliness of skin, and capillarization of skin. The susceptibility to skin cancer caused by solar irradiation is in general inversely proportional to the amount of skin pigment present, as it is the function of the melanin pigment to act as a screen against the ultraviolet rays.

The protective action exerted by melanin is accentuated in the skin of Negroes by the fact that they have not only an increased amount of pigment in the basal layer, in which pigment is found almost exclusively in the skin of whites, but also in large amounts in chromatophoric cells located in the corium, thereby providing an additional protection for the capillaries situated in this region, as well as in the more superficial layers of the epidermis. Marked normal pigmentation of the skin represents one and an important reason for the rareness with which solar cancer of the skin is seen in Negroes (Wells; Hyde; Roffo) as well as in other colored races (Bechet; Gasquet) [Arabs of northern Africa (Ferrer); Chinese (Molesworth); South American Indians (Roffo)]. Additional factors working in this direction are higher normal oiliness and vascularization of the skin of Negroes. The oily layer covering the epidermis does not only absorb a part of the rays, but tends also to reflect the rays at a higher rate than a dry skin which is more often found in white people (Pincussen). Increased vascularization makes for an abundant perspiration, which results in an effective cooling of the skin and, thereby, in reducing the burning effect of solar rays. Schubert contended that the marked capillarization of the skin of Negroes accounted for their ready and appreciable pigmentary response upon solarization.

The important role of pigmentary differences of the skin determining the complexion and, to a certain degree, the color of the hairs and eyes of the various groups composing the white race and influencing their relative sensitivity to solar rays, has been recognized by numerous investigators who studied their influence upon the incidence of skin cancer. Molesworth, for instance, stated that he did not see a single case of solar cancer in persons of Italian extraction, as persons with olive skin and brown eyes were never affected, while Roffo noted that he did not find a case of solar malignancy in any person coming from a stock which had lived for six generations in Argentina. There is, however, a general consensus of opinion that members of the fair complexioned, blond and blue eyed groups of the white race exhibit an increased susceptibility to solar cancer (Bechet; Gasquet; Koelsch; Dubreuilh; Molesworth; Glasunow; Hyde; Corlett; McCoy; Roffo; Duhig). Individuals with a ruddy complexion, accompanied by russet or reddish hair, seem especially to develop solar epithelioma, that is, persons of Irish, Scottish, North German, Scandinavian, Basque descent (Roffo; Molesworth; and others).

In determining the relative susceptibility regarding solar cancer in fair complexioned individuals, the color of the skin was found to be a more dependable indicator than that of the hairs, as a fair skin and blue or grey eyes were not infrequently associated with brown hairs. Corlett found that in a series of cutaneous cancers which he studied that 63 per cent of the lesions occurred in fair skinned and blonde persons; 31 per cent in individuals with a fair skin, but dark hairs; while only 7 per cent were found in persons with dark hairs and dark pigmented skin. Roffo reported similar observations. The importance of the degree of cutaneous pigmentation in white people is reflected in the differences concerning the degree of solar sensitivity displayed by individuals with various complexions. Thus blonde persons are 40 to 70 per cent more sensitive than brunettes to ultraviolet rays (Laurens; Koelsch); Guerrini stated that blonde persons are four times more sensitive to sun-light than individuals with a dark complexion. Ellinger pointed out that these differences were not attributable to variations in the density of the capillary bed, which he found identical in blondes and brunettes.

It may be added that blonde individuals, showing a tendency to freckle are not only more susceptible to solar cancer, but develop this lesion at an earlier age than those having the ability to acquire uniform tanning (Shaw; Auler), as in the former a solar erythema is often not followed by an increased pigmentation and an elevated tolerance to sun rays (Pincussen). It has been suggested that individuals displaying such an abnormal reactivity might harbor a constitutional latent predisposition to xeroderma pigmentosum, indicated by a familial hypersensitivity to solar rays, which may manifest itself in different members of the family by the occurrence of vitiligo, pigmented and non-pigmented nevi in large number, haired warts, ephelides, red-blonde or red

hair, a tendency to sunburn, or inability to tan under the effect of sun rays (Auler).

It may not be a mere coincidence that the majority of cases of xeroderma pigmentosum have been reported from countries of northern Europe (Germany, Austria, England) and relatively few from countries inhabited by a darker pigmented population (Italy, France, Syria) (Councilman and Magrath); [Negroes (Lowenthal and Travell; King and Hamilton); Japanese (Weidman)]. In this connection mention may be made of the demonstration of an apparent relationship existing between the complexion and the function of certain glands of internal secretion. Hamilton and Hubert as well as Hamblen and Cuyler reported that the average daily androgenic titer of true blondes is distinctly lower than that found in brunettes and that androgens (testosterone propionate) may cause hyperpigmentation.

Similar observations concerning the dependence of the degree of sensitivity of the skin to solar and ultraviolet rays upon the amount of cutaneous pigmentation have been made in animals of varying coat color exposed to these actinic agents under environmental and experimental conditions. Drabble found 190 cases of skin cancer among 955,798 head of cattle slaughtered during a period of four years in New South Wales. The animals affected with these neoplastic lesions were either wholly or partly white or light-roan colored, with the exception of three cases in which the cancer originated from scars of burns (brand-cancer). Many of the white animals slaughtered suffered from dermatitis of apparently solar origin.

Relatively frequently melanomatous cancers occur in white and grey horses, that is, in animals having a scanty pigmentation.

Additional evidence concerning the importance of pigmentation for the development of ultraviolet-ray cancerigenesis of the skin has been provided by the observations of Rusch and Baumann, who found that black haired mice required not only a longer exposure before cancers appeared, but developed also cutaneous neoplasms in a lower percentage than seen in animals of an albino strain subjected to the same treatment. It must be mentioned, however, that marked variations exist in the length of the preparatory period needed for eliciting an ultraviolet-ray cancer in animals of the same coat color, but of different species, as the important factor in this connection is not so much the color of the hairs, but the color or pigmentation of the skin. These malignancies are most readily obtained in albino mice. White rats require a longer time of exposure than mice, while rabbits of any color are apparently refractory to the cancerigenic action of ultraviolet rays (Rothmann and Bernhardt; Baumann and Rusch). Abrikosoff and Wail reported the production of an atypical basal cell proliferation in the edge of a surgical ulcer on the back of a rabbit subjected subsequently to an intense ultraviolet irradiation.

It does not seem to be probable that rabbits react differently to ultraviolet

rays from other animals, as Hueper succeeded recently in producing in a strain of white coated, blue eyed rabbits a severe actinic dermatitis with ulcerations, keratoses, pigmentary shifts, scaling, hyperemia, etc., when the animals were shaved with an electric razor in frequent intervals and exposed daily for two hours to the rays of a Hanovia lamp delivering 1,300 microwatts at 30 inch distance. The density of the hair doubtless plays an important role in checking in animals the effect of the ultraviolet rays, upon the skin emphasizing thereby the statement made by Watkins-Pitchford in 1909, that the liability of man to cutaneous cancer is due to the lack of a hairy coat which protects the skin of animals against the carcinogenic action of the sun radiation. Recent observations, made by Hueper in congenitally hairless rats having normally a thick keratinized epidermis, illustrated, on the other hand, the remarkable protective effect exerted by the horny layer against the cancerigenic action of u.v. rays (Blum).

Exogenous Sensitizing Agents. A great number of environmental agents, such as foodstuffs (buckwheat), tar, mineral oils and their derivatives, medicinal substances, such as sulfanilamide, perfumes containing Bergamot oil, may increase the sensitivity of the skin to solar rays or, as in the case of arsenicals, may accentuate the irritative action of these agents. Bechet noted that the degree of exposure to solar radiation depends not only upon the direct irradiation, but also upon the indirect irradiation by reflected rays, as he observed that sun-burns and cancers were more frequent among the inhabitants of regions having a light white clay soil or living on or near large bodies of water, than among people living on a reddish or dark colored soil which absorbs the rays. It is of importance in this respect to recall that sun-light reflected from surfaces of water, snow, ice, white sand, etc., contains an unusually large amount of ultraviolet rays.

Attempts have been made to minimize the value of clinical and experimental observations indicating the cancerigenic effect of solar radiation upon the human skin (Beard, Boggess and von Haam; Luce-Clausen; and others). These investigators argued that the positive results obtained by the irradiation of albino rats and mice with ultraviolet rays were not applicable to man, as the skin of these animals, which are accustomed to a dark habitat, is much more sensitive to solar rays than the human skin and that the doses of ultraviolet rays administered for the production of these experimental solar cancers was moreover disproportionally high in comparison to those encountered by man under environmental or occupational conditions, thus leaving to man a wide margin of safety. It was pointed out that solar cancer was rarely seen in animals (cattle, horses) which were exposed to sun light the year round. Apart from the fact that this conception as well as the interpretation of the evidence is not shared by other investigators (Roffo; Putschar and Holtz), there seems to be little doubt that the data presented in favor of a carcinogenic

action of solar rays upon the human skin, particularly of light pigmented individuals, are satisfactory and convincing, when examined critically.

Issue must be taken with a statement made by Peller and more recently at least partially endorsed by Apperly, in which it is claimed that an exposure of the skin to the carcinogenic solar rays, while resulting possibly in the formation of a cutaneous malignancy, which, however, could be readily cured, conveyed a certain degree of immunity to or resistance against the development of the more dangerous, because inaccessible, cancers of internal organs.

Peller and Stephenson cited in support of their contention the statistical evidence that the cancer mortality of the personnel of the United States Navy between the ages from 25 to 64 was about 50 per cent lower than would be expected from age, sex and color-specific cancer rates of New York for 1930. These investigators claimed that this discrepancy was attributable to the fact that there was a higher frequency of lip and skin cancer among navy men and less internal cancer as compared with the civilian population, indicating that the external, solar cancers acted as a protective mechanism against the acquisition of internal cancers. Similar observations were made by Peller in certain types of industrial workers exposed to light and heat, as this occupational group showed a high death rate from skin cancer and a low cancer death rate from gastro-intestinal malignancy.

While not confirming the existence of such a relationship for regions with a mean temperature of above 42° Fahrenheit, Apperly suggested that the statistical evidence obtained from regions with a mean temperature below 42° Fahrenheit suggested that the less intense solar irradiation prevailing in such localities produced not only a certain immunity to cancer in general, but even to carcinoma of the skin. Whereas Peller and Stephenson proposed to utilize their observations for the prevention of internal cancers by producing intentionally easily curable malignancy of the skin, Apperly stated that it may be possible to reduce the cancer deaths by inducing a partial or complete immunity through an exposure of suitable skin areas to sunlight or to the proper artificial light rays of intensity and duration insufficient to produce an actual skin cancer.

In refutation of these assertions, and as a warning against the practical application of the proposals made by these investigators, it may be pointed out that a reliable and extensive amount of clinical and experimental evidence exists which indicates that the exposure of the skin to a carcinogenic agent does not *reduce*, but *increases* the chances for the development of an internal neoplasm. Warren and Gates, and Warren found that multiple malignant cancers occur more frequently than can be explained on the basis of chance and that this phenomenon may be explained by the action of some factor favoring the development of a malignant condition. Moreover, there was a higher incidence of non-systemic multiple cancers involving the skin and

some internal organ than expected on statistical grounds. König noted in his analysis of multiple primary malignant neoplasms that the most frequent combination is that of a skin carcinoma with a carcinoma of some other part of the body (present in 4 cases of his series of 10 cases of multiple, nonsystemic malignancy). Desaive, Firket, Chevremont and Dardenne suggested that the occurrence of multiple, nonsystemic cancers might be an expression of an exposure to various exogenous carcinogenic agents during life. Roesch found in the small group of German paraffin cancers (18 cases) one instance in which there was in addition to a squamous cell cancer of the forearm, a columnar cell carcinoma of the stomach and a round cell carcinoma of a bronchus. Southam reported as an interesting feature of mule-spinners' cancer of the scrotum, that there were occasionally additional primary cancers in internal organs, such as the stomach, tonsil and the lung, usually appearing subsequent to the removal of the scrotal growth. Southam emphasized that this phenomenon had received little attention from pathologists, in spite of its importance from a medico-legal aspect. English statistics on the relative frequency of various organ cancers have shown, moreover, that occupational groups with a high mortality rate from skin cancer (chimney sweeps) possess also a high death rate from cancer of internal organs.

The experimental evidence available on this subject is extensive and unequivocal in character. The application of various carcinogenic chemicals to the skin of mice (tar, mineral oil, synthetic chemical carcinogens) does not only result in the production of skin cancers, but increases considerably the incidence of pulmonary malignancies and exerts no influence upon the appearance and frequency of spontaneous mammary carcinomas (Lynch; Andervont; Schabad; Bonser and Connal). The conclusion must be drawn that all the evidence not based on notoriously unreliable data from death certificates militates against the existence of an antagonistic relationship between cutaneous malignancy and cancer of internal organs such as proposed by Peller.

VI. AGE

While it has been stated that the skin of man between the age of 20 and 50 years is more sensitive to solar rays than at any other age period (Laurens), this relation is not necessarily reflected in the age distribution of solar cancers because of the presence of numerous complicating and, not infrequently, more important factors. There exists, however, some evidence that this type of actinic malignancy of the skin occurs at a somewhat earlier age period than that at which cutaneous epitheliomas of unknown etiology are found (Roffo). Thus Peller and Stephenson observed that there was a peak in the skin cancer incidence among the personnel of the United States Navy between the age of 20 to 49 years, while a low level was reached between the age of 60 to 69 years, that is, during a period in which the peak of skin cancer among

the civilian population exists. Similar relations are evident from the studies of Sutton and Dubreuilh on the age distribution of solar cancers which are presented in the following table.

AGE DISTRIBUTION OF SOLAR CANCERS

Years	20–30	31–40	41–50	51–60	61–70	71–80	81	
Cases	2	5	6	5	8	1	0	Sutton
		3	18	53	68	46	8	Dubreuilh
Total	2	8	24	58	76	48	8	224

While 92, or 41 per cent, of the 224 cases of solar epithelioma were in the age group of 20 to 60 years, Miescher's series of 516 cases of skin cancer contained 135 cases, or 26 per cent, in this age range (40 to 60 years), with 329 cases, or 74 per cent, present in individuals 61 to 80 years old. Roffo noted specially the occasional occurrence of solar cancer in young persons (in five cases the age was from 27 to 31 years). It cannot be maintained therefore that solar cancer is essentially a manifestation related to the physiological senescence of the skin. It appears to be a pathological reaction to the carcinogenic action of solar rays, which depends, however, not only upon the intensity and duration of exposure to these agents, but also in a remarkable degree on the individual's constitutional susceptibility. These factors, in connection with the age at onset of the (excessive) exposure, determine the age at which the carcinogenic changes become manifest.

VII. LATENCY PERIOD

On the basis of the age range of solar cancer, its latency period has been estimated to vary between 15 to 40 years (Bauer; Büngeler; Miescher). Findlay stated that the exposure period in man was from 10 to 15 years at a minimum. Some of these estimates were in part the result of hypothetical calculations based on the correlation between the normal life span and the latency period of solar or ultraviolet ray cancer of rats and mice. Büngeler thus argued that the latency period of human solar cancer should be at least from 15 to 30 years and possibly longer, because the latency period of this type of malignancy in mice was from 5 to 7 months for the majority of animals, which have an average life span of from 1.5 to 3 years, but appeared to be more sensitive to sun-rays than man. Similar arguments and figures were advanced by Miescher, who stated that the latency period of human solar cancer was from 20 to 40 years, because the average exposure time of mice ranged from 8 to 12 months. Findlay reasoned that the exposure period of man should be at least 10 to 15 years, as the exposure period was at an average

for mice 8 months and for rats 21 months. Beard, Boggess and von Haam calculated on the basis of their experimental data that an exposure to ultraviolet rays lasting 20 hours daily for a period of 18 years would be needed for the production of a cutaneous malignancy in man, because seven months of continuous irradiation with this agent were required to elicit such changes in the skin of rats having a normal life span in which one year was equivalent to 30 years in the life of man.

Apart from the fact that such calculations are based on the entirely unproven assumption that a direct relationship exists between the normal life span of a particular species and the relative length of its reaction time to a certain carcinogenic agent, it must be pointed out that in this special instance such a hypothesis neglects to take into account several important factors (hairy coat, thickness of epidermis, and keratinization, pigmentation, species specific susceptibility), which exert a marked and undeniable influence upon the length of the latency period of solar cancer regardless of the life span of the animal species concerned.

There exist marked and important differences in the anatomical structure of the skin of man and animals affecting the epidermis as well as the cutis (vascularization, fat tissue). The epidermis of man consists not only of a larger number of cellular layers than found in the skin of mice and rats, but it is covered by a layer of keratinized material, which has an important protective function by absorbing a large part of the short ultraviolet rays penetrating into the skin. A cornified layer, on the other hand, is lacking in the skin of the haired animals, which obtain their main protection against the solar rays by the density and thickness of the hairy coat.

Thus it is obvious that in addition to frequent differences in the amount of pigment in various animal species and different individuals, the thickness of the cellular epidermis and the thickness of the horny layer and of the hairy coat, respectively, play important roles in determining the sensitivity to solar rays (Peacock), so that direct comparison between the sensitivity of the human skin with that of animals is not possible without taking these fundamental anatomical differences into proper account (Hueper).

The advocates of the life span theory omit moreover to consider the fact that, for example, rabbits apparently seem to be disproportionally more resistant to solar rays than rats and mice on the basis of a simple comparison of their respective normal life spans. Rusch and Baumann noted that the time of latency of experimental solar cancer of mice depended upon the daily dose of ultraviolet rays administered. If mice were exposed for 60 minutes to a given amount of ultraviolet rays, tumors were present in 15 per cent of these animals after 3.5 months of this treatment, while it took 9 months to obtain this effect when the exposure time was reduced to 10 minutes of irradiation daily, demonstrating thereby that no general conclusions can be drawn from the so-called "average" latency period of ultraviolet cancer of mice and rats,

unless the dose of radiation administered is duly considered, in addition to the other factors mentioned.

VIII. CAUSATIVE MECHANISM

The biophysical and biochemical action exerted by the rays contained in the solar spectrum differs greatly with their respective wave-lengths. While the energy of the infrared and of the luminous rays of the spectrum is transformed mainly into heat in the skin and is responsible for the early erythema developing upon exposure to sun rays by causing a dilation of the cutaneous capillaries to which these rays of long wave-lengths penetrate, the ultraviolet rays are photochemically active rays, that is, they are capable of eliciting photodynamic chemical changes in the material composing the cells and the intercellular substances, which in turn cause the appearance of the delayed and prolonged erythema.

Some of these reactions require the presence of oxygen, others occur in the absence of this element, but depend in part upon the presence of and are modified in type and degree by an endogenous or exogenous sensitizing substance, which often possesses fluorescent properties. *Endogenous* photocatalysts are hematoporphyrin, resulting either from a congenitally faulty metabolism, or being produced as reaction products to various exogenous poisons (lead, trional, sulfonal, veronal, zinc); bile pigments; indolethylamine; or phenylalanine; while *exogenous* photosensitizers are numerous dyes (eosin, methylene blue, rose bengal, acriflavin, erythrosin, neutral red, rhodamin, and other acridin dyes), anthracene derivatives, tar, quinine derivatives, sulfanilamide and derivatives, phytoporphyrin (buckwheat), chlorophyll, arsenicals, gold salts. Some of these sensitizing substances are activated, not only by ultraviolet rays, but also by rays belonging to the luminous part of the spectrum (4,900 to 5,800 Å) (Laurens), and may give rise to the clinical phenomena of light hypersensitivity or physical allergy (Duke; Low), such as hydroa vacciniforme, urticaria solare, or eczema solare (Ehrmann and Perutz; Körbler). Experiments of Rusch, Kline and Baumann have shown that the carcinogenic wave-lengths of ultraviolet radiation are located in the range lying between 2,537 and 3,341 ångstroms, while Roffo placed the range between 2,900 and 3,500 ångstroms.

The photochemically active ultraviolet rays do not penetrate deeply into the skin. The ultraviolet rays of short wave-lengths are absorbed by a layer of hornified material of 30 microns thickness. The longer ultraviolet rays may advance under favorable conditions (thin skin and narrow cornified layer) into the dermis (50 to 80 microns) and may act directly upon the blood and the endothelial lining of the capillaries contained in the papillae (Koelsch; Anderson and Ayres; Harris and Hoyt). The ultraviolet rays are absorbed markedly by sulfur containing and aromatic amino-acids (cystin, tryptophane, phenylalanine, tyrosin). Ninety-eight per cent of the ultraviolet rays of the

sun light (including rays of 2,300 to 3,970 Å wave-length) are absorbed normally by the epidermis, so only very small portions of the chemically and photochemically active rays of the solar spectrum reach the connective tissue, blood vessels and the blood (Koelsch, Peacock).

It is generally assumed that the destructive action of the ultraviolet rays exerted upon the protein matter of the epidermal cells causes the liberation of a vasodilating substance (histamin?) which, in turn, elicits the development of the erythroderma. This primary reaction is followed by three processes: 1) an increased production of melanin in the basal cells, which in normally light pigmented individuals appears in the basal layer and also in the more superficial parts of the epidermis; 2) a stimulation of the cellular proliferation of the basal cells, causing a cellular thickening of the epidermis; 3) an augmented keratoplastic activity of the epidermis, resulting in a thickening of the cornified layer. It is obvious that the three responses provide a greater degree of protection against the actinic energy than that originally present and create an apparent, increased tolerance toward the actinic agent. This is the normal anatomical as well as physical and chemical background of the action of ultraviolet rays, which are the carcinogenic portions of the solar rays, upon the epidermis.

Several theories have been advanced in the attempt to explain the causative mechanism through which these rays elicit the cancerous responses of the epidermal cells. Murray as well as Matthews contended that solar cancers of the skin are the malignant end-products of a long continued epithelial regeneration caused by repeated primary epithelial necroses produced by the sun rays and associated with a nonspecific chronic irritation. A similar opinion was expressed by Putschar and Holtz, who considered the solar epithelioma as a striking example supporting the chronic irritation theory of cancerigenesis, first proposed by Virchow. Abundant clinical evidence provided by chronic occupational dermatoses of various origin and lacking carcinogenic tendencies in addition to the numerous observations made in connection with the experimental production of cancer by chemicals has shown conclusively that simple, nonspecific chronic irritation is neither a fundamental nor an essential causative factor of carcinogenesis, while it is often associated with the development of malignant processes.

Körbler suspected that hematoporphyrin plays a certain causal role as a photodynamic sensitizer in the production of cancer of the skin, because he could demonstrate a bright red fluorescence in numerous skin cancers, which he considered as indicative of the presence of hematoporphyrin. Apart from the fact that a red fluorescence is not a satisfactory proof of the presence of hematoporphyrin, it is important to note that individuals with a hematoporphyrinemia do not always exhibit an increased sensitivity to solar rays and that congenital hematoporphyrinemia is not accompanied by cutaneous manifestations resembling those seen in xeroderma pigmentosum, which is a disease, resulting

from a congenital hypersensitivity to solar rays, of unknown causation and characterized by the ultimate development of multiple solar cancers of the skin. There exists, on the other hand, some experimental evidence which suggests that the carcinogenic action of tar can be accelerated by the simultaneous effect of a sensitizing substance (Büngeler).

Bauer, who asserted that ten times the therapeutic dose of ultraviolet rays administered over a sufficiently long period is necessary to elicit a carcinogenic cutaneous response, proposed that the ultraviolet rays act like the roentgen- and radium rays by causing a photodynamic, chromosomic cellular mutation in one cell which serves as the source of the malignant growth. This theory completely disregards the circumstances accompanying solar carcinogenesis. Inasmuch as this theory assumes that the cellular mutation is brought about by the action of a certain quantum of actinic energy upon a cell or a definite part of a cell, the law of chance requires that occasionally such an event should take place during a very early part of solar irradiation, so that the development of a malignant growth should ensue, however rarely, after a relatively short time of exposure. Clinical as well as experimental experience does not support such a mechanism. To the contrary, the cancerous condition appears always to be the product of a prolonged exposure to the actinic energy, which, in turn, causes not only multicellular changes, but often also multifocal cellular alterations affecting cellular morphology, pattern and interrelation and assuming a permanently malignant character after a long latency period.

It is well to refer in this connection to a statement made recently by von Euler, Günther and Forsman who noted that much evidence has accumulated indicating that the cellular carcinogenic mutations caused by rays, including ultraviolet rays, are not caused directly by the action of the actinic energy, but are actually chemical mutations, resulting secondarily from the production of carcinogenic substances in the tissue under the effect of the rays.

It appears only natural that the attention of several investigators looking for a chemical cause of solar carcinogenesis was directed first to cholesterol, a substance present in cells and tissue fluids which is not only chemically closely related to certain synthetic carcinogens, but which also undergoes chemical changes of a photodynamic nature when exposed to ultraviolet rays.

Roffo, who is the chief proponent of a carcinogenic action of a photodynamically activated and modified cholesterol, contended that the exposure to sun rays causes an increase of the cholesterol content in the irradiated parts of the skin, while the carcinogenic effect is exerted by a photodynamic conversion of a part of this cholesterol into a cancerigenic substance which shows absorption lines located in the same regions as those characteristic for the synthetic carcinogenic phenanthrene derivatives.

Whereas Knudson, Sturges and Ryan confirmed the observations of Roffo concerning the increase of the cholesterol content of the irradiated skin of white and piebald rats, they pointed out that this increase was most marked in the

region of the face and much less in the skin of the back, and was mainly attributable to an elevation of the cholesterol esters. These investigators were uncertain, whether these reactions were connected with the development of cancers of the skin involving chiefly the nose, ears and region of the orbit. Baumann and Rusch, however, concluded from their experiments on mice, rats and guinea pigs exposed to ultraviolet rays that these agents increase the cholesterol content in the exposed skin of the rat only, but not that of the mouse or guinea pig. Mice, receiving a diet containing 2 per cent cholesterol, did not develop cancers of the skin more rapidly than controls kept on an ordinary stock diet. These investigators concluded, therefore, that no relations appeared to exist between the cholesterol content of the blood, liver, kidney, ears, or skin and the production of skin tumors by exposure to ultraviolet rays. The alleged causal role of cutaneous cholesterol in this respect remains controversial.

The pigmentary reactions of the skin preceding and accompanying the development of solar cancers, as well as several other occupational canceroses of the skin, aroused the suspicion that possibly melanin or its aromatic components might be involved in the production of skin cancer (Baader). It is not likely that hyperpigmentary changes are significant in this respect, as such reactions follow a great number of chemical irritations without leading to a malignant complication. Moreover, solar cancer affects mainly those individuals with a pigmentary deficiency and abnormally low pigmentary reactivity. It may be possible, on the other hand, that ultraviolet rays may act upon aromatic protein decomposition products and may form new substances by photosynthesis, photolysis, polymerization or condensation, which may possess carcinogenic properties. Baudisch and Hoschek thus found that indol and alphamethyl indol are polymerized by solar rays under the formation of anthranilic acid. While the aliphatic aminoacids, glycocoll, leucin, alanin, asparagin, are not changed by light, the aromatic aminoacids, tyrosin and tryptophane, undergo oxidation. Rideal and Mitchell showed that a monomolecular film of stear-anilide, ($C_6H_5NHCO\ [CH_2]_{16}$), is decomposed by photolysis into aniline and stearic acid, suggesting thereby a mechanism by which aromatic groups may be split off from a protein molecule by ultraviolet rays (2,480 Å and 2,537 Å) (Carpenter), as the benzene ring in this compound is located in the side chain and attached indirectly to the alpha carbon of the acid, imitating therein the type of peptide linkage of aromatic groups in protein molecules. It may be also of importance that glucuronic acid compounds are decomposed by ultraviolet rays, inasmuch as glucuronates of aromatic compounds represent the detoxified metabolites.

Attention may be given also to the fact that solar rays reflected from isotropic surfaces are partially polarized. While it has not yet been shown that polarized light exerts a different biological effect than unpolarized light (Pincussen; Keller), it has been suggested that circularly polarized light may

initiate an asymmetrical synthesis based on a Cotton effect in the ultraviolet. Thus, Jaeger pointed out that, as sunlight reflected by the surface of the sea is always in part elliptically polarized as the result of the terrestrial magnetism, the reaction velocity for a photochemical action upon a certain substance may be different from that when the antipodes are attacked by the circularly or elliptically polarized light of oppositely directed rotation, if the wave-length of maximum light absorption by a given substance is at the same time the optimum for the photochemical action. This investigator argued that such conditions might be responsible perhaps for the one-sidedness of the synthesis in the living cell (majority of proteids are levo-rotary; bile acids and sugars are dextro-rotary). These thoughts of Jaeger concerning the influence of polarized reflected light upon the metabolic activities of living matter assume some importance in connection with the causation of solar cancer, as this disease is most common in individuals who are exposed not only to direct irradiation, but also at the same time to a great deal of reflected and evidently in part polarized radiation. The recent claims of Kögl and his co-workers concerning the occurrence of dextrorotary aminoacids in the protein molecules of cancer cells gives additional emphasis to this aspect of solar irradiation and its possible connection with the causative mechanism of solar cancer of the skin.

In view of the fact that Wels contended that there arises in the skin during an irradiation with ultraviolet rays a substance having the qualities and the function of sulfhydryl bodies, and considering that Hammett proclaimed the sulfhydryl group as the exclusive intracellular catalyst of cellular proliferation, this aspect of ultraviolet ray action upon the skin will be discussed briefly, especially as disturbances of the sulfur metabolism have been incriminated by several investigators in the production of cancers.

The claim of Wels just mentioned is based on the observations that there is a liberation of sulfhydryl substances when an albumin solution is irradiated with ultraviolet rays in a nitrogen atmosphere, and that there is an increase of the sulfhydryl groups in excised and irradiated pieces of skin. The significance of this evidence is perhaps best indicated when it is pointed out that there is normally for some time an increase of free sulfhydryl groups in excised and dying and decomposing tissues (Bierich and Kalle).

Inasmuch as the production and stability of sulfhydryl groups depends upon the character of the environmental conditions, it is important to note that the irradiation of an alkaline albumin solution with ultraviolet rays results in an acidification of this solution, while the same treatment given to an acid albumin solution causes its alkalinization (Kroetz).

Moreover, Lieben and Molnar; Shoji; Hueper and co-workers; and others have shown in various experiments with watery solutions, as well as with biological material, that the exposure of sulfhydryl containing substances to ultraviolet rays causes their oxidation and upon prolonged exposure their de-

struction. This effect may be attributed in part to the generation of hydrogen peroxide in the living irradiated tissue which oxidizes the –SH groups contained in aminoacids first into the –SS– groups and then into sulfonic acids (RSO_3H) (Schoeberl).

The hyperemic reaction caused in the skin under the influence of solar or ultraviolet irradiation favors rather an increased oxidative metabolism than a reduced one. While the degenerative effect exerted by the ultraviolet rays upon the superficial cell layers of the epidermis apparently stimulates the process of keratinization, the increased blood supply brought to the germinative layer in connection with cellular degeneration products activates the cellular proliferation in the basal cells. Disturbances in the sulfhydryl equilibrium of the epidermis, caused by the solar rays, do not seem to be connected in any specific fashion with the development of the solar cancers, but may be involved in this process through the detoxicating action of sulfhydryl groups.

Jungeblut and Feiner proposed that an overdosage of ultraviolet rays produces an excessive destruction of ascorbic acid, causing thereby an exhaustion of this detoxicating agent in the body, and may initiate a derangement of vitamin C metabolism.

It is apparent from the foregoing discussion of the causative mechanism of solar cancer that this aspect is more a field for speculation than of information.

IX. SYMPTOMATOLOGY

Precancerous solar dermatoses are either due to a congenital and often hereditary hypersensitivity and usually appear in young individuals (xeroderma pigmentosum) not necessarily exposed to excessive amounts of solar rays, or represent lesions acquired by a prolonged and extraordinarily intensive irradiation in normal, adult persons. The macroscopical and microscopical changes characterizing these two types of dermatoses show many similarities with each other as well as with the cutaneous alterations of the experimental dermatoses of mice and rats produced by a prolonged solar or ultraviolet irradiation. The cutaneous actinic lesions undergo in the course of time a certain succession of changes until ultimately they assume a malignant character.

Following prolonged and repeated exposures to solar rays, sensitive individuals, after the passing of the primary transitory erythematous or erysipelatoid reaction, develop a distinct cutaneous hyperemia associated with the appearance of ectatic, tortuous vascular ramifications which sometimes assume an angiomatoid character and which are usually accompanied by the development of a more or less diffuse and discrete brownish spotting and freckling. Parts of the exposed skin intervening between the pigmented areas may exhibit a whitish color and a smooth, atrophic scarry appearance, caused in part by the occurrence of a pigmentary shift resulting in local deficiencies of melanin. These telangiectases and atrophies of the skin, which occur only in individuals with a defective pigmentary protective reactivity and thereby

abnormal susceptibility to solar irradiation, are in general less markedly developed in the acquired dermatosis (xeroderma pigmentosum tardium) than in the juvenile, congenital form of this disease. The vascular dilatations are in part compensatory phenomena, following the obliteration of adjacent capillaries. They may persist for a long time, thus indicating that the ectatic condition is the result of a more or less irreversible colloid-chemical alteration in the capillary endothelium. The skin becomes hard, dry and scaly during the developmental stage of these capillary changes.

With the progress of the chronic cutaneous alterations, there occur epidermal thickenings (hyperkeratoses) and scabs, which are located mainly at the temples, forehead, nose and external ear as well as on the back of the hand and on the forearm. These keratotic lesions are circumscribed, brownish, flat and later often verrucous and indurated excrescences which have a greasy crust when located on the face and scalp, or are rough and hard when situated on the hands. They may be fixed to the underlying tissue, which usually shows a deficiency of fat tissue. Sometimes the verrucous lesions merge, forming larger plaques from which cancers may develop ultimately. Multiplicity of the neoplastic lesions is the rule. Both cornified squamous cell carcinomas and basal cell cancers (rodent ulcers) may ensue from the precancerous lesions. The squamous cell keratotic cancer is the most frequent type of solar malignancy. The fully developed form of malignant solar dermatosis thus represents an epitheliomatosis or cancerosis of the skin.

Similar observations have been made in connection with the development of experimental solar and ultraviolet ray cancer in rats and mice. Beard, Boggess and von Haam; Roffo; Putschar and Holtz; and others reported that after the first two months of exposure the hairy coat of rats became ruffled, the hairs began to fall out and the skin showed eczematous lesions on the back, at the base of the tail, and on the ears. The brown scabs which appeared were scratched off frequently. Later on, the skin became dry and smooth. Then followed the development of crusts on the inflamed parts of the skin. Finally, ulcers formed at the sites of these crusts. Following a period characterized by a more or less complete repair of these lesions, the hairs started to grow again abundantly, but were often arranged in tufts. The margins of the ears became thickened and keratotic, the eyelids were swollen, while ultimately the eyeballs were destroyed. The malignant transformation of the keratotic papillomata and warty thickenings was ushered in by an ulcerative breakdown of the particular lesion.

X. HISTOLOGY

The acute radiation reaction is characterized by the appearance of polynuclear leucocytes in the vessels of the papillae and of the upper cutis. The cornified and granular epidermal layers remain morphologically unchanged, while the cells of the prickle cell layer exhibit a colloidal degeneration, accompanied

by an intense stainability of the cytoplasm. The basal cells show an intracellular edematous swelling and a lowered stainability of their nuclei. Soon afterwards, with the onset of the ensuing regenerative proliferation, large vesicular cells appear with numerous mitotic figures and distinct nucleoli in the basal layer. At first these newly formed cells do not contain any pigment, while the pigment originally present in the basal cells has been shifted into the scale covering the basal cells. A subsequent increase of dopaoxidase in the epidermis is followed by a simultaneous appearance of considerable amounts of melanin pigment in the basal cells as well as in dendritic cells located in the cutis.

It may be pointed out in this connection that the accumulation and distribution of pigment granules in the basal layer and in more superficially located parts of the epidermis as well as in dendritic chromatophores of the cutis are not characteristic of a solar hyperpigmentation, but are found in the skin of whites under various pathological conditions, such as arsenical and tar melanoses, roentgen-melanosis, melanotic skin around varicose ulcers, or scleroderma and represent a normal condition in Negroes (Keller). There appear in some individuals, on the other hand, areas containing markedly decreased amounts of melanin (leukoderma).

In addition to these localized hyperpigmented and hypopigmented areas, capillary dilatations are seen in the papillary body and corium followed by the appearance of perivascular round cell infiltrations and swelling of the endothelial and perithelial cells accompanied sometimes by vascular obliteration. These initial morphological responses of the skin to an exposure to solar rays, while fundamentally the same in normal and hypersensitive individuals, are more pronounced and more persistent in the hypersensitive person.

On the basis of and subsequent to these acute and subacute actinic changes, there develops in the skin of the susceptible individual, upon repeated, prolonged and intensive irradiation, a series of pathological lesions which have a certain sequence in their appearance. The cutaneous manifestations which follow are partly of atrophic, partly of hyperplastic nature. Smooth, pigmented papules, which form a part of the atrophic lesions, show a lack of papillae. The basal cells are heavily pigmented, while a marked degree of irregularity in size and shape of the cells prevails in the transitional layer. Spines and intercellular bridges are lacking often in the spinous cell layer. The cells seem to be embedded in large vacuoles. Acantholysis exists. The cytoplasm of the epithelial cells, on the other hand, is compact and the nuclei are dense. The thickness of the epidermis is reduced to 3 to 4 layers of cells. The vessels of the cutis are normal.

The white atrophic lesions show a lack of melanin, especially in the basal cell layer, and a thinning of the prickle cell layer. There are fibrosing changes, characterized by a rarefaction of the elastic tissue, with a swelling and thickening of the preserved elastic fibrils in the derma. The collagenous fibrils are clumped and in the process of dissolution, leaving a hyaline mass.

The hyperplastic and hyperkeratotic manifestations display a broadening and deepening of the papillae. Epithelial strands project into the subcutaneous tissue. Small plump proliferations of basal cells extend into the subepithelial connective tissue. The cells of the superficial epithelial layers exhibit a marked polymorphism and contain, occasionally, mitoses. There are vacuolated, polygonal cells, giant cells, as well as small cystic cavities resulting from cellular lysis. The vacuoles usually surround the nuclei. The cornified layer is thickened and keratinizations occur within the upper epithelial layers. Sometimes acanthosis is considerable. While a regular granular layer is in general absent, there are cells containing large eleidin granules. The connective tissue beneath these wart-like formations exhibits an inflammatory cellular reaction, dilated capillaries and perivascular lymphocytic, plasma cellular and mast cellular infiltrations. The sebaceous glands are intact, whereas the sweat glands may show cystic cavities. While there is a lack of vessels in the connective tissue underneath the atrophic lesions, numerous large, thin walled, congested veins, apparently replacing capillaries, and forming plexus-like arrangements, are found beneath these hyperplastic reactions. The active cellular proliferation of the hyperplastic lesions, as well as their ultimate malignant transformation, seem to depend upon the presence of a sufficient vascularity in the connective tissue underneath. The vascularity and the associated blood supply, however, are by themselves not the actual proliferation stimulating agents, but only serve to make such a reaction possible. It is remarkable in this connection that the ensuing cancerous growth extends in the direction where a collateral circulation is present, while avoiding areas where an impaired blood supply prevails, that is, the scars (Kreibich; Councilman and Magrath; Bering and Barnewitz; Sutton; Pincussen; Dalons and Constantin; Unna; Dubreuilh; and others). The malignant sequelae are typical cornified squamous cell carcinomas or basal cell cancers.

Similar changes are seen in the skin of rats and mice subjected to solar or ultraviolet rays. Chronic inflammatory processes, such as small ulcers, leucocytic infiltrations of the cutis, and marked congestion of the blood vessels prevail during the early weeks of the treatment. The epidermis is thickened and forms ridges, while there is, at the same time, some new formation of hair follicles and sebaceous glands. This stage is followed by the development of markedly thickened and hyperkeratotic epithelium, particularly around the follicular orifices. Small, round, intraepidermal epithelial nodules appear during this phase. The basal cells display a mild proliferative activity by forming small processes extending into the cutis. The new formation of hair follicles and sebaceous glands is markedly increased. Chronic inflammatory processes are present in the cutis. The next developmental stage is characterized by the appearance of everting and infiltrative epithelial proliferations. The keratotic papillary excrescences consist mainly of spinous cells, while the granular epithelial cells are practically absent. At the base of these epitheliomas, plump

epithelial cords invade a connective tissue containing swollen and hyalinized collagenous fibrils and crumbling elastic fibrils. There appear isolated, not always sharply demarcated, proliferations of atypical basal cells containing numerous mitoses. Keratinizing epitheliomas and folliculo-epitheliomas develop ultimately from these atypical epithelial hyperplastic lesions. In addition to the two mentioned most common types of experimental solar carcinomas, there occur sometimes cancers resembling, morphologically, basal cell cancer of man. Other epitheliomas are composed of spindle-shaped epithelial cells giving to the tumors a sarcomatoid appearance. These sarcomatoid cancers are very similar to anaplastic carcinomas observed in mice after tar applications.

The number of cancers in the irradiated series of animals, as well as in the individual animal, increases with the duration of exposure to the carcinogenic actinic agent. Once started, the tumors grow progressively, even after cessation of irradiation (Rusch and Baumann). The evidence presented shows unequivocally that solar cancer of the skin does not originate from any embryonic epithelial germs in the skin, but arises from independent, newly formed, epithelial proliferations elicited in the epidermis under the influence of the actinic energy.

XI. PREVENTIVE AND PRECAUTIONARY MEASURES

Light sensitive individuals should avoid prolonged exposures to intense solar radiation. The wearing of wide brimmed hats and colored shawls, as well as the application of ointments and creams containing light absorbing agents to the exposed parts of the skin, may help to reduce the destructive and carcinogenic action of the actinic energy upon the epidermis. The following substances are used as active ingredients of light absorbing ointments: naphthol sodium sulphonate; lanolin; extract of the cortex of horse chestnuts; titanium dioxide; ichthammol, methyl salicylate (Bachem and Fantus).

XII. MEDICO-LEGAL ASPECTS

Occupational solar cancer of the skin is not recognized in any country among the compensable occupational diseases.

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b. ROENTGEN-RAYS AND RADIOACTIVE SUBSTANCES

I. TECHNOLOGICAL AND HISTORICAL NOTES

The discovery of the existence of highly penetrating rays, emitted by certain types of chemicals or artificially produced in vacuum tubes through which an electric current is conducted, was made shortly before the turn of the century. In 1895, Wilhelm Conrad Röntgen reported that invisible, highly penetrating, electro-magnetic rays (x-rays or roentgen-rays) were emitted from a solid substance, when it arrests in a highly exhausted vacuum glass tube (Crookes's tube) the electronic rays given off by the cathode while an electric current is passed through the tube. This discovery gave rise to the development of the roentgen-tube.

In the original tubes used by Röntgen, the x-rays were emitted from those parts of the glass walls of the tube where the cathode rays were arrested, and therefore caused a more or less diffuse radiation. The presently used and more perfected tubes have a curved cathode built so as to release directed and focused rays which strike upon a specially constructed target placed at an angle to the cathode rays. The target consists of a metal possessing a high melting point (tungsten), because a great amount of heat is generated when the cathode rays are converted into x-rays, which are reflected as a directed beam from the narrow focus of the target. The higher the voltage of the electric current used in the production of the cathode rays, the shorter and the more penetrating are the x-rays that they generate. The early roentgen-tubes used a rather low voltage and produced a soft type of x-rays. In more recent years, with the increasing improvement in the quality of roentgen-tubes, high volt-

ages can be employed, and thus hard and more penetrating roentgen-rays are obtained.

When roentgen-rays pass through and are partially absorbed by any kind of material, such as the glass wall of the tube or the walls and furnishings of the room in which the roentgen-tube is operated, they give rise to the production of secondary, softer rays (scatter-rays). In spite of the vast improvements made in the manufacture of modern roentgen-tubes, their walls still give off secondary roentgen-rays which are undesirable for technical as well as hygienic reasons. The tubes are therefore enclosed in a shield which absorbs the secondary rays of the walls of the tube and which permits the main beam of roentgen-rays to escape through a properly placed hole. This arrangement, however, does not eliminate the production of secondary scatter-rays from objects which are in the path of the beam of the roentgen-rays. The penetrating power of these scatter-rays depends directly upon the hardness of the original roentgen-rays.

The discovery of radioactive rays was made by H. Becqérel in 1896, when he observed that uranium salts emit spontaneously and continuously a penetrating radiation (gamma-rays), which later on was shown to be of a shorter wave-length and of much higher penetrating power than the roentgen-rays, but of similar physical character. Pierre and Marie Curie in 1899 succeeded in isolating from pitchblende (uranium ore) the salts of radium, which displayed a much higher radioactivity than uranium salts. Subsequent investigations resulted in the discovery of a large number of radioactive elements, which generate radiating energy of three different types (alpha-rays, beta-rays and gamma-rays), released during the disintegration of the original elements and their transformation into other elements.

Roentgen-rays as well as radioactive substances are extensively used in medicine for diagnostic and therapeutic purposes and have an ever increasing application in a variety of industries (spectroscopy; detection of defects, cracks, blowholes in castings, of defects in alloys from faulty mixture, of corrosion in cables or gas cylinders, of defects in reinforced concrete, weldings, golf balls, rubber heels). Roentgen-rays are used to examine eggs for freshness, vegetable foods for mineral adulterants, grain for the presence of weevils, and in shoe stores to test the fit of shoes. It is important to note that very penetrating rays are used in the examination of metallic objects and thick specimens (Hunter).

II. EXPOSURE

Injurious effects upon the skin through an exposure to roentgen-rays may be brought about through contact with the primary rays contained in the beam coming from the roentgen-tube or with the secondary scatter-rays emitted from the wall of the tube and from the objects absorbing primary rays. Whenever high voltage rays possessing a high penetrating power are used, such exposures may involve not only individuals who are in the room where the roentgen-

rays are generated, but also persons present in adjoining quarters, if the walls, ceiling and floor of the radium- or roentgen-room are not properly insulated with lead or other absorbing material preventing the penetration of primary and secondary roentgen-rays.

Often repeated occupational exposures to usually more or less small doses of roentgen-rays sustained over prolonged periods occur in several occupations. There are first the individuals engaged in the manufacture and testing of roentgen-tubes who are apt to be subjected to such hazards (male and female workers engaged as technicians, engineers, physicists, testers) (Laborde and Leclercq). Roentgen-rays are produced during the manufacture of roentgen-tubes, especially when the tubes are evacuated, a procedure requiring several hours, during which an electric current of high tension is passed through the tubes (bombardment of the thermionic valve). Workers engaged in this operation are exposed to roentgen-rays if not protected by lead shields of proper thickness corresponding to the tension of the electric current applied. During the early years of the roentgen-tube industry when the dangers connected with the exposure to roentgen-rays were not adequately known and appreciated, it was a common practice among the men testing the new roentgen-tubes for proper hardness of the rays produced to use their left hand for a test object. Occupational exposure to roentgen-rays is sustained by physicists, engineers and mechanics engaged in the construction, installation and repair of roentgen-apparatus. Similar and even greater hazards existed, particularly during the early period of roentgenology, for physicians, dentists, technicians, and nurses using roentgen-rays for diagnostic and therapeutic purposes. In spite of numerous and effective precautionary measures introduced, the danger from exposure to secondary rays, especially during the performance of fluoroscopic work, still persists to a certain degree, while the introduction of shielded tubes, lead glass screens, and remote control has removed largely any exposure of the operators to direct irradiation, particularly during the administration of roentgen-therapy.

The application of roentgen-rays in modern industry for radiographic and spectroscopic examinations has widened greatly during recent years the circle of potentially exposed individuals, such as metallurgic engineers, plumbers, builders, ammunition experts, textile chemists, crystallographers, physicists, industrial engineers, rubber chemists, automobile tire testers, experts of pearls, diamonds, and paintings.

Some of the apparatus designed for industrial purposes are portable apparatus which are set up wherever needed, while others are large, stationary roentgen arrangements of industrial laboratories using powerful, high voltage apparatus. The degree of hazard to which the operators of roentgen-equipment of industrial laboratories are exposed evidently depends to a large extent upon the working conditions present, that is, the type and amount of precautionary measures taken or possible under the circumstances prevailing. The

incidence of chronic roentgen-dermatitis and roentgen-cancer among these occupational groups during the coming years will reflect properly whether or not the lessons learned by the medical profession have been utilized by individuals who may not be prepared to appreciate fully the slow and insidious destructive biological action of an invisible physical agent.

An occupational exposure to radioactive substances is found among the personnel of manufacturing laboratories and of medical therapeutic radium-departments, especially if radioactive preparations are handled with bare hands or with insufficiently long applicators, or when radioactive material is handled inaptly and too slowly, causing an undue exposure of the finger tips. However, in view of the very powerful and penetrating nature of the gamma-rays emitted by some of the radioactive elements, proper protection of these parts is not possible, and harmful exposures result whenever radioactive substances are handled too often and over too prolonged periods.

III. GEOGRAPHICAL DISTRIBUTION AND INCIDENCE

Because the injurious biological effects exerted by the penetrating rays emitted from roentgen-tubes and radioactive substances were not known, and the danger connected with their contact was not appreciated, it was not long after the discovery of these radiating agents that the first chronic precancerous cutaneous lesions (chronic roentgen- and radium-dermatitis) were observed among the manufacturers of roentgen-equipment and the medical operators of roentgen-apparatus and radium-preparations. The number of individuals sustaining such injuries because of lack of any precautionary measures was considerable during the early period of the use of these actinic agents, but the incidence of such harmful effects has decreased considerably in more recent times following the introduction of adequate protective measures. The following is a list of investigators who reported the occurrence of cases of occupational, accidental or medicinal chronic roentgen-dermatitis: Marcuse (1896); Oudin, Barthélemy and Darier (1897); Richer and Londe (1897); Kienböck (1900); Beck (1902); Hallopeau and Gadaud (1902); Unna (1904); Mühsam (1904); Wyss (1906); Dessauer (1907); Kassabian (1907); Schümann (1907); Dean (1908); Lindenborn (1908); Deutschländer (1908); Rawling (1909); Porter (1909); Coenen (1909); Albers-Schönberg (1910); Rosenbach (1910); Hesse (1911); Bichler (1914); Ribbert (1914); Gavazzeni and Minelli (1915); Dautwitz (1922); Rowntree (1922); Dohan and Kienböck (1922); Dubreuilh and Chaussé (1925); Cole (1925); Flaskamp (1930); Holthusen (1931); Fuss (1932); Turchini (1932); Bordier (1933); Béclère (1933); and Laborde and Leclercq (1936); Saunders and Montgomery (1938).

Reports on the occurrence of chronic radium-dermatitis were published among others by Walkhoff (1900); Holznecht and Exner (1903); Guyot (1909); Walkhoff (1913); Giesel; Gudzent and Halberstaedter (1914);

White (1916); Ordway (1916); Dautwitz (1922); Friedländer (1922); Jakoby (1929); Schürch (1930); Béclère (1937); Teleky (1937).

It is not known, even approximately, how many of these cases of chronic roentgen- and radium-dermatitis ultimately resulted in cutaneous malignancies. Mention, however, must be made of the fact that, while the occurrence of these precancerous lesions has been reported from numerous countries, cancerous sequelae have been recorded only from a limited number of countries.

The first case of occupational roentgen-cancer, as well as the first fatality from this disease, was reported from Germany (Frieben, 1902, and Albers-Schönberg, 1919). The victim was a manufacturer of roentgen-tubes. Additional cases from Germany were described by Sick (1903, 3 cases); Unna (1904, 2 cases); Schümann (1907, 1 case); Coenen (1909, 1 case); Herxheimer (1909, 1 case); Rosenbach (1910, 1 case); Hesse (1911, 13 cases); Bichler (1914, 3 cases); Frangenheim (1914, 1 case); Tilling (1915, 1 case); Depenthal (1919, 1 case); Brezina (1929, 6 cases); Krause (1930, 1 case); Flaskamp (1930, 1 case); Walischewski (1932, 3 cases); Gütig (1933, 1 case); Staemmler (1937, 1 case).

The total number of occupational *roentgen*-cancers of the skin observed in Germany is approximately 40 cases; it is not certain whether several of the cases listed were counted twice. Droschl in 1933 added the only case of an occupational *radium*-carcinoma which has been noted in Germany. It is significant that the hazard has decreased greatly in recent years. During the first 20 years of roentgenology, there were 28 reports of professional roentgen-cancer, while there were only 12 in the second period of twenty years, although the use of roentgen-rays has increased enormously.

Miescher in 1925 reported 4 roentgen-cancers from Switzerland but he did not state whether or not they were of occupational origin. Hesse (1911) mentioned the occurrence of one occupational cancer by roentgen-rays in Luxemburg. The same investigator referred to two occupational roentgen-cancers in France. Gougerot reported a third one in 1911. The first record of this type of neoplasm from England was published in 1903, when two cases were observed. Porter and White mentioned a third case which was published in 1904 in the *Medical Record*. Foulterton reported an additional case in 1905. Dean stated in 1908 that there were at that time 20 to 30 cases of severe chronic radiodermatitis among the pioneers of roentgenology in England, of whom four were affected by carcinomas. Rawling as well as Evans added one more case each in 1909. In the same year Rowntree stated that eleven cases of occupational roentgen-cancer existed in England. A new case of this professional neoplasm was reported by Scott in 1911. In his review on this subject, Hesse (1911) noted that 13 cases of this disease had been recorded from England up to that time. This statement was confirmed by Rowntree in 1922, who noted that two new cases had occurred since. Rowntree expressed

the hope that by that time probably all of the early cases of professional roentgen-dermatitis had developed into malignancies and that for this reason this type of occupational neoplasia would cease to exist. Unfortunately, Rowntree's expectations were not fulfilled, because in 1927 O'Donovan added a new case to the list of English martyrs of science. Seven years later Handley published an additional case of professional roentgen-cancer, to be followed in the next year by a report of a new case published by Hunter. Bridge and Henry noted in 1928 that there was not a single case of industrial roentgen-cancer on record in England. Wakely added in 1927 to this list one case of pure professional radium-cancer. The total number of occupational roentgen- and radium-cancers in England is thus approximately 20. The first and only case of this occupational disease was reported from Russia in 1932 (Vigdortschik).

The only cases of roentgen- or radium-cancer on an occupational basis recorded from Asia originate from Japan. The first case was reported in 1931 by Yamakawa and Shimada, and was followed four years later by eight additional cases (total of nine cases) published by Miyaji.

South America (Argentina) has contributed so far two cases of this professional neoplasia (Roffo, 1932).

The great majority of the American cases were reported from the United States. Porter and White recorded in 1907 the occurrence of 8 cases of occupational roentgen-cancer. Two years later this number was increased to 25 by Porter. The review of Hesse (1911) referred to 26 American cases of professional origin. Dible and Morison added a new case in 1925. Two years later Cole reported from his own practice 9 cases of roentgen-dermatosis of which two were clinically and a third one histologically malignant. In addition to these therapeutic cases Cole had knowledge of an occupational roentgen-cancer in a physicist, who was not under his care. Mulsow (1931) and Adair (1934) each contributed one case of occupational genesis to the American list.

An appreciable number of occupational roentgen-cancers were added by Saunders and Montgomery (1938), who surveyed a total of 259 cases of chronic roentgen- and radium-dermatosis observed at the Mayo Clinic during 1930 to 1934. There were 26 physicians and dentists in this group, one of whom showed malignant lesions, while of the 233 therapeutic cases of roentgen-dermatitis only 17 had malignant manifestations. It is of medico-legal interest that two of the therapeutic cases developed a roentgen-cancer following the therapeutic application of roentgen-rays because of an occupational dermatitis, establishing thereby a secondary or indirect type of occupational roentgen-cancer. Cole and Driver added one more case of professional roentgen-cancer present in a dentist to the American list. McNeal, Ward and Willis reported the only case of professional radium-cancer of the skin (1923). There are approximately a total of 45 cases of occupational roentgen- or radium-cancer on record from the United States.

The total number of reported cases of occupational roentgen- and radium-cancers of the skin from all countries is approximately 125, of which three cases only were caused by an exposure to radioactive substances. It is needless to state that this figure is evidently appreciably below the actual one, as the data concerning the incidence of this medical professional disease are notoriously incomplete and inaccurate (Hess; Cole; Ledoux-Lebard; Rosenbach). This deplorable situation has not been ameliorated unfortunately by the recent compilations of Brown and of Meyer concerning the deaths of roentgenologists, technicians, nurses, and engineers from an occupational exposure to roentgen- or radium rays. Brown collected 28 fatal cases of occupational roentgen-cancer which were observed in the United States between 1895 and 1935. Meyer listed in addition to Brown's series the names of 166 martyrs, many of whom died from malignant sequelae of an actinic causation. The situation existing, especially during the early years, is illustrated by a statement made by Rowntree in 1922, who noted that practically every roentgenologist who suffered from roentgen-dermatitis during 1899 to 1906 utlimately developed cancer. It may be mentioned that Saunders and Montgomery emphasized that their recent figures on the incidence of chronic radiodermatitis and roentgen-cancer could not be considered as final, as the latency period in some of their cases was too short for a malignant complication to develop.

In addition to these cases of occupational roentgen- and radium-cancer there exists an ever increasing number of therapeutic carcinomas of this genesis. Dohan and Kienböck estimated that there were several hundred cases in 1922. If this estimate is correct, it would indicate that the majority of these cases have not found their way into the literature. The following case reports were published: Wyss (1906) one case; Lindenborn (1908) two cases; Rosenbach (1910) one case; Klemperer (1911) one case; Hesse (1911) twenty four cases; Bichler (1914) one case; von Haberer (1921) one case; Hazen (1921) one case; Appelrath (1925) one case; Lane (1930) one case; Laborde (1931) three cases; Holthusen and Englmann (1931) one case and thirty-nine cases collected from literature; Fuss (1932) one case; Müller (1935) eight cases; Saunders and Montgomery (1934) eighteen cases; Pohl (1939) two cases.

Holthusen pointed out that 23 of the 39 cases of his series, which included cases recorded up to 1931, have been observed before 1910, that is, they had been produced at a time when the carcinogenic hazard connected with the medicinal use of roentgen-rays was not yet fully recognized and appreciated; however, they originated also in a time when this agent was not so generally used. While the estimate made by two competent and authoritative European roentgenologists, Dohan and Kienböck, apparently is not based upon references in the literature, but upon their knowledge of the actual situation existing, one is led to ask: How high does the incidence of therapeutic cancer run

in the United States, when 18 cases are observed during 5 years in one of the leading clinics of this country.

An appreciable number of the therapeutic roentgen-cancers developed on the basis of lupus vulgaris and lupus erythematosus subjected to roentgen-treatment. Numerous other disease conditions reacted in a similar way following a prolonged exposure to roentgen-rays (psoriasis, eczema, trichophytosis, pruritus ani and vulvae, hypertrichosis, benign and malignant tumors, tuberculous osteomyelitis) (Saunders and Montgomery; Klemperer; Hazen; von Haberer). In several of these cases roentgen-rays were used by incompetent operators for the removal of excessive hair for cosmetic reasons (Lane; Saunders and Montgomery).

IV. AGE

The information available on age distribution of roentgen-cancers often shows no distinction between occupational and therapeutic neoplasms. Hesse stated that the age range in his series of 29 cases was from 28 to 66 years, the average being 49.5. The age range in Brown's series is from 35 to 74 years, the average age is 44 years. The following table presents the age distribution of 35 cases of occupational roentgen-cancer.

AGE DISTRIBUTION OF OCCUPATIONAL ROENTGEN-CANCERS

Years	20–30	31–40	41–50	51–60	61–70	71–80	Total
Cases	1	18	9	6	0	1	35
Brown's series	0	4	8	9	3	2	26

The following table brings for comparison the age distribution of 24 therapeutic roentgen-cancers, using mainly data by Holthusen and Englmann.

AGE DISTRIBUTION OF THERAPEUTIC ROENTGEN-CANCERS

Years	10–30	31–40	41–50	51–60	61–70	71–80	Total
Cases	3	8	4	9	1	0	25

The range of the therapeutic roentgen-cancers is from 9 to 67 years and the average age is 43 years.

Both types of roentgen-cancers exhibit a marked shift into the younger age groups, thereby demonstrating that the age of the individual at the time of exposure, together with the intensity of irradiation, determine the manifestation time, which is unrelated to the presence of any physiological senile changes of the skin. The majority of skin carcinomas of unknown etiology occur in individuals from 50 to 70 years old.

V. SITE

The localization of the roentgen- and radium-cancers reflects very definitely the organs of most intense exposure. The following table lists the distribution of the occupational neoplasms:

SITE OF OCCUPATIONAL ROENTGEN- AND RADIUM-CANCERS

Fingers	Left Side	17 Cases
	Right	9
	Unknown	8
Dorsum of Hand and Wrist	Left	14
	Right	15
	Unknown	5
Arm	Left	0
	Right	1
	Unknown	2
Head	Lip	1
	Cheek	2
	Nose	1
Trunk	Back	2
	Chest	2
	General	2
	Breasts	2
	Abdomen	1

It has been asserted by Hunter, by Cole and by others that the neoplasms of roentgenologists and their assistants are located mainly on the left hand, as this hand is exposed, especially in fluoroscopic work, while the right hand is said to be more often the site of tumors in engineers and mechanics. The following table contains the distribution of cancers of the fingers and hands in physicians and engineers:

DISTRIBUTION OF CANCERS ON HANDS AND FINGERS ACCORDING TO OCCUPATIONS

Hands and Fingers	Right	Left
Engineers	8	9
Physicians	12	20

These figures suggest that the left hand and fingers of physicians are more exposed than the right one, while in engineers and persons in similar occupations such a difference is not apparent from the evidence available.

It is characteristic of cutaneous changes in roentgenologists that the neoplastic lesions and their precursors involve the tips and dorsal aspects of the

fingers, hands and wrists, stopping sharply where the cuff of the sleeve begins and has offered some protection against the destructive action of the rays. The volar surfaces of the fingers, hands and wrists remain intact. Dermatotic and neoplastic roentgen-lesions of the face are rarely encountered in roentgenologists, while the face, chest, back, and extremities, in addition to fingers and hands, are not infrequently the site of roentgen-cancers in technical workers, such as engineers, mechanics, and physicists, as this occupational group is exposed more generally than the medical profession. While there are five cases of roentgen-cancer affecting parts of the skin outside of the fingers and hands among engineers and mechanics, only two similar cases are found among roentgenologists, who, moreover outnumber the technical group by a ratio of 2 to 1.

The therapeutic roentgen-cancers, on the other hand, show a different local distribution, which, according to Holthusen and Englmann, does not correspond with those parts of the skin most often exposed to injury by roentgen-rays, especially the skin of the abdomen. These two investigators presented the following tabulation of the sites of therapeutic roentgen-carcinomas in relation to the sites of roentgen-injuries of the skin (Groedel and Lossen).

SITES OF THERAPEUTIC ROENTGEN-CANCERS

Region	Roentgen-Cancer	Roentgen-Injuries
Head	10	8
Vulva	3	1
Arms	1	1
Neck	1	7
Extremities	9	35
Back	5	17
Chest	5	8
Testes	1	1
Abdomen	8	23

Hazen reported an additional case located on the eyelid, and Laborde listed two therapeutic cancers of the face and one of the hand.

Holthusen and Englmann noted that the skin of the head seems to be especially predisposed to a cancerous development. This predisposition of the facial skin is likely not a constitutional property, but represents an acquired quality possibly caused by previous exposures to contributory agents such as solar rays and tar preparations.

VI. MULTIPLICITY

Multiplicity of roentgen-cancers is observed very frequently (Coenen: 27 per cent of cases; Hesse: 31.5 per cent; Walischewski: 29 per cent). The

multiplicity is most often of the successive type, less frequently of the simultaneous variety. The occurrence of multiple tumors is as a rule systemic and restricted to the skin of the fingers, hands and wrists. Hesse stated that the appearance of 4 to 6 roentgen-carcinomas in one individual was not rare. Tumors of hands and fingers of both sides were observed in 13 cases. The 2 cases of alleged roentgen-carcinoma of the mammary glands were bilateral tumors (Depenthal; Vigdortschik). In the case reported by Depenthal neoplastic lesions affecting the fingers of both hands preceded the appearance of the mammary malignancies. Multiple cancers involving the hands and fingers, and other parts of the body, such as back, chest, cheek, nose, and ankles were found in 13 cases. One roentgenologist developed more than twenty cancers, while one engineer had approximately one hundred cancroids scattered over the trunk, hands, forearms, forehead and temple.

The 3 occupational radium-cancers affected the fingers and hands (in 1 case both sides, in 1 case each right or left side, respectively).

VII. OCCUPATIONAL DISTRIBUTION

The occupations followed by the roentgen-cancer cases are known in 87 instances; 61 belonged to the medical profession (physicians, dentists, roentgen-assistants, laboratory technicians, nurses, medical roentgen-photographers) and 26 were engaged in the production and sale of roentgen-tubes and apparatus (engineers, physicists, mechanics, technicians, and salesmen).

The following table presents details of the occupational distribution of roentgen- and radium-carcinomas of the skin.

OCCUPATIONAL DISTRIBUTION OF ROENTGEN- AND RADIUM-CANCERS

Medical Group Cases		Technical Group Cases	
Physicians, Dentists	50	Engineers, Physicists	8
Nurses, Technicians	11	Mechanics, Salesmen	18
Total	61		26

It is interesting to note the shifts in the professional distribution of roentgen-cancer which have taken place in the course of the past 40 years. During the early period, when neither the manufacturing group, that is, the roentgen-engineers and mechanics nor the medical group, that is, the physicians, technicians and nurses used any or very defective and inefficient precautions and therefore received rather massive exposure to relatively soft rays upon the hands, arms and face, both groups contributed comparatively equally to the number of roentgen-cancers. In a compilation prepared by Dean in 1908 com-

prising 19 cases, 14 of the cases were in physicians, 1 in a medical assistant, and 4 were among manufacturers and technicians of roentgen-apparatus. The ratio between medical and technical cases stood at that time at 3 to 1. When Hesse analyzed his collected cases in 1911, this numerical relation had shifted markedly in favor of the technical group, as there were 26 members in the medical group and 24 members in the technical group, a ratio of approximately 1 to 1. In the American series of Brown there are 18 roentgenologists, 1 roentgen-technician, 4 physicists and 5 manufacturers of roentgen-tubes and other equipment.

Following the introduction of effective protective measures and improvements in the manufacturing technique of roentgen-tubes, the number of chronic roentgen-injuries in the manufacturing group decreased when compared to the medical group, because physicians could not apply the protective measures as effectively as the engineers (Dohan and Kienböck, 1922). Friesleben (1929) stated that an inquiry made in German hospitals and industrial establishments concerning the incidence of roentgen- and radium-injuries showed that 94 per cent of these lesions occurred in the 125 hospitals queried, while only 6 per cent of the total number were reported from the 14 industrial establishments queried. This condition seems to have undergone a change in Germany during recent years, as a note published in 1938 in the *Klinische Wochenschrift* mentioned that during 1935 to 1936 roentgen-injuries were found almost exclusively among industrial workers and seldom among attendants of roentgen- and radium-laboratories and hospitals. No information on these matters is available from other countries.

It is doubtful whether these numerical relations between the two professional groups reflect the actual conditions accurately or even approximately. It appears not unlikely that the publication of the occurrence of roentgen-cancers among workers in the manufacturing and sales departments of manufacturers of roentgen-apparatus is even less complete than among members of the medical profession (Walischewski).

VIII. SEX

The sex distribution of occupational roentgen- and radium-cancer heavily favors the male sex. There were 73 cancers in men and 4 in women (ratio approximately 18 to 1). Two of the women were physicians, one was a roentgen-assistant and one a nurse.

IX. EXPOSURE TIME

The exposure time of professional roentgen-carcinoma varies greatly with each individual case and depends, apparently, to a great extent upon the type, duration and intensity of the individual exposures sustained, which in turn determine the developmental speed of the summation effect repre-

sented by the radiodermatitis and, ultimately, the malignant neoplasia. Walischewski stated that the average time of exposure was 11 years, while Hesse noted that it was approximately 9 years (range 4 to 14 years). Porter reported an exposure time of from 3 to 11 years (most often 5 to 7 years), and Teutschlaender found the exposure time of 55 cases of occupational roentgen-cancer to vary between 3 and 21 years. Hunter mentioned a range of 3 to 21 years. Koelsch noted that the shortest exposure time on record was 4 years. The following table presents the exposure time of 34 cases of roentgen-cancer of occupational genesis.

EXPOSURE TIME OF OCCUPATIONAL ROENTGEN-CANCER

Years	3–5	6–10	11–15	16–20	21–25	26–30	31–35
Cases	4	10	8	6	3	2	1

The exposure time for two radium-cancers was 17 and 25 years, respectively.

The developmental period, that is, the time which elapses between the first irradiation and the clinical manifestation of the cancerous growth, shows still wider variations. Ledoux-Lebard noted that the developmental period was in general from 8 to 11 years. Saunders and Montgomery stated that in their mixed series of occupational and therapeutic roentgen-cancers from one and a half years to eighteen years elapsed between the initial exposure to roentgen-rays and the appearance of the neoplastic response. These variations correspond closely to the differences observed in the development of radiodermatitic changes in different individuals, as Dohan and Kienböck found that from 6 months to 7 years may pass before the first morphological changes of chronic roentgen-injury of the skin becomes apparent.

Miescher noted a latency period of from 1.5 to 2 years for the appearance of roentgen-atrophies of the skin, which plays an important role in the symptom complex and finally leads up to the appearance of cancerous reactions. However, many years may go by before any malignant transformations may become apparent in a skin affected by chronic roentgen-dermatitis. This development may ensue, on the other hand, in spite of a complete cessation of exposure to the injurious agent as soon as the first radiodermatitic changes become apparent. The latency period in such cases extends from a few years to one to two decades. Hesse observed a latency period ranging from 1 to 11 years (average 7.25 years). Teutschlaender noted a latency period (incubation period: time elapsing from appearance of first sign of radiodermatitis and the clinical evidence of cancer) of 9 years.

The following table presents the latency period observed in 36 cases of roentgen-cancer arranged according to years (average latency period 7 years).

LATENCY PERIOD OF ROENTGEN-CANCERS

Years	1	2	3	4	5	6	7	8	9	10	11	12
Cases	1	2	3	1	3	10	1	2	3	6	3	1

Saunders and Montgomery found the principle well established that "the more extensive the injury, the more likely the development of cancer thereon", that is, third degree burns carry a higher chance of future malignant complication than second degree burns and these, in turn, possess greater malignant potentiality than first degree burns. This observation indicates that no absolute values as to latency or developmental periods can be established, as these depend obviously to a marked degree upon the amount and duration of roentgen-exposure received and the type of injury produced.

X. SYMPTOMATOLOGY

The development of a roentgen-carcinoma is always preceded by a chronic roentgen-dermatitis or chronic roentgen-dermia, inasmuch as inflammatory processes play a subordinate role in this condition(Béclère). The chronic precancerous roentgen-injury, in turn, may follow an acute roentgen-dermatitis when relatively massive and unfiltered roentgen-rays are applied to the skin, while a primary acute reaction is absent in cases subjected to small doses of roentgen-rays acting repeatedly over a prolonged period. During the early days of roentgenology when no adequate precautions were taken, the development of roentgen-cancers was preceded for these reasons by both acute and chronic cutaneous changes. Later on, following the introduction of protective measures, which more or less eliminated the exposure to direct radiation and large doses of roentgen-rays, the first signs of a roentgen-injury were immediately of chronic character, making, however, a delayed appearance.

Acute Roentgen-Dermatitis. An acute roentgen-dermatitis starts with the development of an erythema appearing a few hours after the irradiation. The early and primary erythematous reaction recedes to some extent during the first week and is followed by a more persistent, main erythema during the second or third week. This erythroderma presents a sharply delineated, erysipelatoid, intensely red and diffuse discoloration of the irradiated skin, such as seen with thermic burns. Simultaneously, there is a loss of hair, if haired parts were exposed. If the roentgen-burn is severe, the devitalized tissue finally breaks down and an ulcer is formed, which shows little healing tendencies and proves to be eminently chronic. With lesser burns there occurs a gradual reduction in the intensity of the erythema and a drying of the vesicles. With the recession of these acute reactions, the roentgen-injury enters the chronic stage.

Chronic Roentgen-Dermatitis. A chronic roentgen-dermatitis, which is either

a sequela of an acute reaction or is the direct response to the summation of repeated, small, suberythemal doses, is characterized by the concomitant presence of atrophic and hypertrophic changes associated with pigmentary disturbances.

Inasmuch as a chronic roentgen-dermatitis is not a stationary condition, but is continuously changing in the degree and type of its cutaneous manifestations, attempts have been made to distinguish between different stages of this process. These classifications, however, have met with certain difficulties, as lesions which are considered as characteristic of different stages may be found not infrequently at the same time in different parts of the radiodermatitic skin. While subjected to certain limitations, classifications are essential for gauging, at least approximately, the degree of injury existing.

Saunders and Montgomery have proposed the following grouping of roentgen-burns based upon symptoms indicating their relative severity: "Injuries of the first degree consisted of the cutaneous changes of atrophy, sclerosis, telangiectasis, pigmentation, alopecia and diminished sweat and sebaceous function—any, several, or all of these, but without evidence of keratoses or ulcers; injuries of the second degree comprised any or all the changes of the first degree plus the presence of small ulcers (from a few millimeters up to 7.5 cm. in diameter) or numerous keratoses; injuries of the third or most severe degree were injuries presenting the features just mentioned for the other two degrees, plus the presence of large ulcers (more than 7.5 cm in diameter)." It may be mentioned that the skin changes, produced by a mild exposure to the radiating agent causing a slight swelling, melanosis, dryness, loss of elasticity and hair, appearance of tiny warts and of comedo-like formations, may be reversible, unless the exposure is continued. Under such circumstances they become irreversible and progressive (Schürch).

Following the main erythematous stage, sometimes there develops a livid discoloration of the swollen skin caused by vascular and circulatory disturbances of the cutaneous vessels before an increased diffuse or spotty pigmentation appears. Upon the application of cold, the skin may seem to resemble chilblains indicating that deep seated hypotonic vessels participate in the production of the reactive, passive hyperemia. While a melanotic state is produced even after the mildest type of irradiation, such pigmentary changes are usually transitory. The pigmentary disturbances which accompany more severe types of chronic roentgen-injury may persist, on the other hand, for many years or may become permanent. The hyperpigmentations observed under such circumstances are usually local and spotty in type and are accompanied by restricted depigmentations so that the skin assumes a mottled appearance (leuko-melanoderma (Miescher)). The skin then shows brown pigmented areas, reddish white, hyperemic, well vascularized areas, and whitish, atrophic looking, anemic areas.

Simultaneously with these pigmentary changes, there occurs an impairment or complete inhibition of the functional activity of the appendiceal skin glands

(sweat glands, sebaceous glands) and loss of hair (alopecia). Whereas these effects are transitory in first and second degree burns, they are permanent with third degree burns, in which the glandular elements are destroyed by the severe roentgen-ray effect. As the result of these functional disturbances, the skin becomes dry, scaly, rough, dull and covered with a white dust (Cole). There develops at the same time an atrophy of the epidermis. The thinning of the skin results in a more marked red color of the blood vessels. With a progressive flattening of the normal ridges and wrinkles, the skin becomes smooth, glassy, translucent, delicate and inelastic, covering a reduced connective tissue. Later on, the skin may assume a bacon-like, sclerodermic appearance of board-hard consistency, or it may become increasingly atrophic and exhibit a senescent, dried out, wrinkled, and parchment-like character. The tactile sensitivity becomes reduced with the development of these changes, while the sensivity to thermic influences becomes greatly accentuated. Often there appears a sensation of tension and heat, together with itching in the affected parts.

Not infrequently the fingertips become pointed as the result of marked atrophic changes. The nails become deformed, dry and brittle and develop longitudinal and transverse ridges, or may fall off entirely, being replaced later by a highly distorted rudimentary nail formation. The ribbed nails break off easily, fissure readily and assume a dirty brown appearance. They tend to loosen from the nailbed, thicken subsequently and finally turn into shapeless masses. Subungual hemorrhages and telangiectases develop sometimes and paronychias are a frequent complication. Marked subungual hyperkeratoses, which often appear, particularly after the handling of radioactive substances entailing an exposure of the fingertips, lift the nails from their matrix.

In addition to these atrophic and degenerative lesions in the epidermis, there also occur various types of hyperplastic and hypertrophic changes of local and diffuse keratotic character, which give to the skin a harsh touch. Two different types of keratotic lesions are observed in the chronically injured skin (Unna): (*1*) *hard warts* which are sharply circumscribed verrucous keratotic excrescences, often displaying an inflamed and painful base; they are usually multiple, irregularly distributed in areas showing only moderately atrophic changes; they grow slowly, some are dry, others are crusted; spontaneous regressions occur rarely; (*2*) *calluses*, which are elevated, shiny, stripe-like keratotic indurations of grey to greyish-yellow color, alternating sometimes with brown, hyperpigmented spots and located usually in the margins of nails and in the interdigital folds; they are frequently painful, containing in their base small subepidermal abscesses; their lamellated horny layer may desquamate spontaneously but is readily reformed, or it may slough, leaving an ulcerative defect, which bleeds readily. Ulcers develop also in the verrucous hard hyperkeratoses, which show a tendency to fissure and then to break down. The ulcers have a coarsely granular surface covered by a dirty greyish red exudate. Their firm, yellow margins are formed in general by

overhanging and elevated hyperkeratoses, falling off steeply toward the floor of the ulcer, but fading out gradually toward the periphery.

The atrophic portion of the skin furnishes a third source of roentgen-ulcers. This atrophic skin is highly sensitive to many kinds of physical and chemical traumas that are often of very mild and common types, such as soap, disinfectants, photographic chemicals, mechanical or thermic injury. Rhagades are formed, particularly in the region of the knuckles. When these break down, ulcers result which heal either slowly, and break open again, upon the least provocation, or they are refractory and may persist for years. These torpid, atonic ulcers are painless in the beginning, but later may produce excruciating pains. After years of duration their edges may become indurated and elevated, forming cauliflower-like, keratotic protrusions (Rosenbach; Béclère).

Concomitant with these changes which involve mainly the epidermis, there appear newly-formed dilated, tortuous and varicose capillaries in the subepidermal tissue, which are sometimes rather coarse and at other times more delicate, forming spider-like arrangements which involve smaller or larger areas of the injured skin. Telangiectatic pre-existing capillaries may participate in the development of these vascular abnormalities. The capillarectases are often found beneath a leukodermic epidermis, producing thereby lesions resembling the white spots present in the skin of xeroderma pigmentosum. While these vascular changes are no constant phenomena, they may follow even after very mild types of roentgen-injury. They may be considered as a part-phenomenon of the chronic congestion existing in the chronic roentgen-dermatitis and are related to functional and anatomical changes of the walls of deeper vessels. Deep seated fibrotic changes in the periarticular connective tissue are responsible for the swelling of the finger joints and for their ankyloses which are observed not infrequently in severe injuries.

The malignant growths, which arise in a skin showing these lesions, originate most often either from hyperkeratotic warts or in the hyperplastic margins of chronic roentgen-ulcers of varying derivation (Bordier). Atrophic parts furnish less often the basis of a malignant growth.

Saunders and Montgomery pointed out that carcinomas may develop occasionally in healed roentgen-ulcers many years after their apparent quiescence, starting usually in those parts of the scar which are composed of a thin, telangiectatic tissue. Warty or cone-shaped hyperkeratoses, which may be considered benign as long as they remain stationary, must be suspected of undergoing a malignant change when the horny mass is rapidly reformed after removal and when an infiltrative fixation of their base becomes apparent, accompanied by a rapid increase in size, throbbing pains and a tendency to slough, leaving either an ulcer, which shows no tendency to heal and excretes a fetid, malodorous exudate, or a delicate red skin.

Cancers arising in an atrophic part of the skin originate usually in leukoplakia-like areas in which a retracted spot ulcerates and becomes surrounded by a callous margin representing a malignant growth (Hesse). Enlarged

regionary lymph nodes may be the result either of infectious or inflammatory reactions or are the seat of secondary neoplastic deposits. Primary multiplicity of tumors is frequent and may be simultaneous or successive in character affecting sometimes widely separated areas. The malignant development in the chronically injured roentgen-skin is set off not infrequently by some kind of traumatization (Halberstaedter).

While the changes observed after prolonged occupational exposure to radioactive substances are fundamentally identical with those found in connection with chronic roentgen-injury, the type of exposure brings about certain peculiarities in the location and character of the preneoplastic and neoplastic responses which deserve special mention.

The fingertips of persons handling radioactive substances show the most marked effect of the radiating energy because they are the most exposed parts of the body. After a relatively short period of exposure they show a flattening of the ridges of the skin and become painful and numb. With progressive atrophy, the fingertips become pointed and the skin smooth and shiny (Teleky; Droschl; Becquérel). The gradually increasing indistinctness of the cutaneous ridges ultimately leads to complete obliteration of the original finger prints. The pads of the fingertips lose their elasticity so that pressure marks on their surfaces persist for a few seconds. The nails develop dystrophic changes, while the cuticle turns dry and white. With a subsequent thickening of the epidermis, wrinkles and cracks appear in the horny layer of the dry, scaly, parchment-like skin of the tips. Hyperkeratoses develop beneath the nails (Jakoby) as well as on the dorsal and volar sides of the fingertips. A certain awkwardness in picking up objects results from the numbness of the fingertips (Ordway) which later develop an increased sensitivity to thermic influences, especially heat, as well as a throbbing sensation. Warty hyperkeratoses, which sometimes fall off spontaneously or can be pried off and whose development may be accompanied by radiating pains, may involve the more proximal parts of the fingers, the interdigital folds, the back of the hands and the forearms, where they are usually associated with pigmentary disturbances (Giesel; Friedländer). The hyperkeratoses of the fingertips necrotize ultimately and form small, highly painful, indolent ulcers, which slowly extend and finally involve the entire area of the fingertip. The thumb and the second finger of the right hand are most often affected for obvious reasons. Cancers may arise on the basis of the warty growths and of the ulcers and assume a mushroom-like appearance.

XI. HISTOLOGY

Acute Roentgen- and Radium-Dermatitis. The character, degree, reversibility, persistence and progressiveness of the cutaneous changes found in an acute roentgen-dermatitis depend upon the intensity of the exposure to the radiating energy. They are of importance in connection with the anatomical changes leading to the development of roentgen-cancer, as they are not

infrequently the initial lesions in the skin which, after having passed through a chronic phase, may provide the soil for the malignant reaction, without being modified or intensified occasionally by any additional or prolonged exposures to the biologically active rays which elicited the acute reaction. The nature and sequence of these acute cellular responses and their chronic sequelae have been studied and described by a number of investigators (Unna; Miescher; Dohan and Kienböck; Wood; Windholz; Baermann and Linser; Gassmann; and others).

The first reaction elicited by the radiating energy in the skin and causing the initial phase of the primary erythema consists of a paralytic dilatation of the cutaneous vessels, especially the terminal arterioles, but also of deeper and larger vascular branches including veins. Within a few days there appear a few signet-ring cells in the epidermis as well as scattered or occasionally crowded mitotic figures in the basal layer. Some of these mitoses show a clumping and derangement of chromosomes. The epidermis as well as the papillary body become edematous, while a mild to moderate perivascular round cell infiltration develops in the cutis and a leucocytic infiltration fills the vascular lumina.

After the recession of the primary erythematous reaction and during the development and duration of the secondary main erythema, that is, two to three weeks after the irradiation, a marked cellular polymorphism appears in the epidermis. Many cells contain two to three hyperchromatic nuclei, sometimes of different size, or in association with nuclear fragments. Some of the nuclei possess two or more swollen nucleoli. There is evidence of beginning amitotic divisions, such as rod shaped and indented nuclei. While multinucleated cells are present throughout the epidermis, they are particularly frequent in the basal layer. Atypical mitoses, on the other hand, are scarce. It is remarkable that these pathological changes do not affect uniformly the epidermis, but are found in an irregular fashion scattered throughout this tissue, often appearing to be crowded in certain spots.

Whereas the lesions in the cutis may be of minor character after mild irradiation and may consist then of a few perivascular leucocytic infiltrations and scanty swollen endothelial cells of blood vessels, they are of more serious nature after intense irradiation. In addition to leucocytic exudation, vascular congestion, swelling and desquamation of endothelial cells, which are associated in places with the formation of thrombi, there develops a honeycomb-like, vacuolar degeneration and interstitial edema of the smooth muscle tissue of the vascular walls accompanied by a loosening of the elastic membranes. Obliterative endarteritic and endophlebitic intimal proliferations may appear later involving especially the deeper vessels. These changes may be followed in the veins by a hyaline necrosis of the media and intima. The lymphatics are often dilated (Wood) and later may become obliterated (Gassmann) by the proliferation of endothelial cells. There is a swelling of the collagenous

fibrils in the cutis, while the connective tissue cells are swollen and have hyperchromatic nuclei.

During the transition of this second phase into the third and last phase of the acute reaction, when the erythema fades away and may disappear completely, there occurs a narrowing of the epidermis, which then is composed of hypertrophic cells and numerous multinucleated cells. There is marked cellular and nuclear polymorphism. The cells of the basal layer contain an increased amount of melanin, while the more superficial epidermal layers display hydropic degenerative changes, melanin pigmentation and evidence of keratinization. There are no inflammatory reactions in the cutis, which contains scanty multinucleated fibroblasts and endothelial cells as well as pigmented melanophores.

The third phase of the acute roentgen-dermatitis, which begins usually, according to Miescher, 6 to 7 weeks after the irradiation and which passes directly over into the chronic roentgen-dermatitis, is characterized by morphological manifestations similar to those found during the second phase, if the exposure was *mild*. If the irradiation was *severe*, the reactive processes maintain a progressive character. While the number of epidermal cellular layers is reduced still further, there is a marked increase in cellular and nuclear irregularity. Multinucleated cells may become so frequent that every second and third cell may contain several nuclei. Some nuclei possess little chromatic material, but large nucleoli. There are numerous normal and pathological mitoses, which are especially frequent in the neighborhood of intra-epidermal foci of liquefaction necrosis. During the latter part of this phase, a new basal layer is formed which consists of densely crowded and rather small, deeply staining cells containing numerous normal mitoses. This newly formed germinative layer lifts the polymorphous original stratum malpighii from its base. With the gradual disappearance of multinucleated giant cells in the stratum granulosum, there appears in some foci a hydropic swelling of the more superficial epithelial cells which are transformed into large vesicles. A hyaline necrobiosis of the epithelial cells is observed in other parts of the epidermis. These ribbon-like, hyaline foci are infiltrated by phagocytic cells and surrounded by mitotic figures containing epithelial cells. The newly formed epithelial cells composing the new thickened epidermis are not quite normal, as they are often hypertrophic and deficient in chromatin.

The cutis exhibits during this time a minor degree of edema and a few perivascular round cell infiltrations in addition to epithelioid cells. The endothelial cells of blood vessels are sometimes swollen, while homogeneous, anuclear areas or areas composed of muscle cells with several and distorted nuclei are found at times in the venous walls.

There may occur a gradual and slow return to normalcy, if the skin is not too severely damaged, especially in its vascular aspects. A more persistent and progressive course ensues after an intense and massive irradiation result-

ing in ulceration (roentgen-necrosis) as well as after repeated and prolonged exposure to small doses which continue and accentuate the pathological reactions in the irradiated skin, thereby causing the development of a chronic roentgen-dermatitis.

Chronic Roentgen-Dermatitis. The histology of chronic roentgen-dermatitis has been made the subject of intense and detailed study by numerous investigators (Unna; Schürch; Wolbach; Cole; Hesse; Béclère; Flaskamp and Wintz; and others). While no complete agreement exists concerning the presence and the role of the vascular changes observed during this stage of roentgen-injury, the presence of atrophic, degenerative, hyperplastic and normal epidermal areas side by side in the affected skin, giving it a mottled appearance, seems to be undisputed (Flaskamp and Wintz).

The atrophic areas show beneath a reduced cornified layer a narrowed epidermis lacking the normal papillary pegs and covering in a straight line a dense, thickened, fibrous or hyalinized corium, which replaces the normal collagenous connective tissue and which does not contain any glandular appendiceal organs (sebaceous glands, hair follicles, sweat glands). The erector muscle of the hairs have a vacuolated cytoplasm and the capillaries beneath the epidermis are dilated and ectatic. Depending upon the intensity of the irradiation which caused these changes, there occur various vascular lesions in the deeper part of the cutis and subcutis. After the exposure to relatively massive doses, such as were seen during the early period of roentgenology, several investigators (Wolbach; White; and others) observed the occurrence of extensive endarteritic and endophlebitic changes, of perivenous fibrosis and of vascular obliteration in the deeper parts of the skin. There were thrombosed telangiectases in the corium, which contained moreover subepidermal necroses of varying size. These, however, were surrounded not infrequently, according to Wolbach, by epithelial processes extending from a hyperplastic epithelium overlying the necrotic foci.

Unna, on the other hand, emphasized the fact that in chronic roentgen-dermatitis the tissue lesions are more pronounced in the epidermis than in the vascular elements of the skin, in contrast to the conditions met with in acute roentgen-dermatitis (Schürch). These investigators reported that the deep veins and arteries as well as the superficial capillaries were dilated and engorged, but were structurally intact, indicating thereby that the vascular changes were more of a functional and distributory nature and not of an anatomical type. Cole also stated that the deeper vessels, while having thickened walls, were not sclerosed. The telangiectases, which were considered by some investigators as compensatory responses resulting from the obliterative processes in the deeper vessels, were related by Unna, in part, to a mechanical compression of deeper veins by the increasing cicatricial fibrosis of the cutaneous connective tissue. However, the telangiectases present in those parts of the skin free from any appreciable scarring were regarded as the

result of a new formation of dilated capillaries involving mainly their venous parts and representing the superficial extensions of obliquely ascending, more deeply situated, branches of larger capillaries. Hesse emphasized that there occurred an absolute as well as relative increase of capillaries beneath the epidermis of the skin in chronic roentgen-dermatitis, and even White commented on the fact that in certain areas the deep cutaneous vessels were hyperplastic, dilated and conspicuous by their caverno-angiomatous character.

While the differences concerning the nature and extent of the vascular lesions seem to have their plausible reason in expositional factors, the vascular manifestations seem to provide mainly the nutritive background for the development of the important hyperplastic epidermal responses. There exists a diffuse or localized broadening of the cornified layer in these lesions. Whereas the stratum lucidum is absent, the granular and spinous layers are thickened and their intercellular connections are loosened by an intercellular edema. Large, vacuolated cells containing nuclei flattened out against the cell walls are found in the malpighian layer. The basal cell layer shows varying degrees of disarrangement and possesses foci of deeply staining cells. Solid epithelial pegs extend from the sharply demarcated basal layer into the subepidermal connective tissue, which contains occasionally a few round cell infiltrations. The prickle cells present in the central portions of the tongue-like extensions dipping into the corium sometimes possess numerous mitoses. In some hyperplastic lesions the epithelium assumes the morphological characteristics of cellular irregularity typical of a malignant growth without displaying, however, its infiltrative qualities. With the onset of invasive proliferation and the disappearance of the sharp demarcation toward the connective tissue, the histologically malignant roentgen-reaction of the epidermis ensues.

These morphological changes are not necessarily identical with the actual biological cancerization of these cells, which may either precede or follow upon the histological cancerization (Schürch). It is estimated that cancerization occurs ultimately in approximately 40 per cent of the individuals with chronic occupational roentgen-dermatitis (Wood).

Roentgen-Cancer. Roentgen-cancers develop usually from the primary hyperplastic and hyperkeratotic warts or from the secondary hyperplastic verrucous growths in the margins of ulcers. While Eller claimed that large scars resulting from third degree burns are most likely to develop cancers, Schümann pointed out that scars rarely become the site of roentgen-cancers. However, atrophic areas may border on cancerous ones. In addition to the actually malignant lesions, there are observed in the chronically injured skin small foci of diffusely infiltratively growing, highly irregular epithelial cells of sarcomatoid appearance, resembling the "anaplastic carcinoids" seen in the skin of rabbits and mice after tar applications and in the vesical mucosa of dogs after the administration of beta-naphthylamine.

The origin of the roentgen-cancers is apparently often multicentric, the

various locally closely related foci merging ultimately to form a single growth (Hesse). The cancerous areas show often an abundant capillary supply and are usually surrounded by a dense zone of lymphocytes, plasma cells and leucocytes. The malignant growth extends mainly in the direction of the well vascularized parts of the cutaneous tissue, as the fibrous scar tissue in atrophic areas impedes its progress (Wood). In spite of the fact that melanosis is a characteristic feature of chronic roentgen-dermatitis, the carcinomatous proliferations are free from any pigmentary activity, resembling in this respect several other occupational cancers (solar, arsenic, tar, pitch) which are accompanied by cutaneous melanosis (Porter and White).

The great majority of roentgen-cancers are cornified squamous cell carcinomas, but basal cell cancers and intermediate types have been observed occasionally (O'Donovan; Coenen; Bichler; Fuss; Yamakawa and Shimada). Corresponding to their high degree of differentiation, the squamous cellular roentgen-cancers have, as a rule, a malignancy grade I or II. Cancers with a malignancy grade III or IV occur occasionally and are usually associated with a severely damaged skin (Adair; Saunders and Montgomery). Multiple carcinomas may display varying degrees of histological malignancy.

XII. SUSCEPTIBILITY

Endogenous as well as exogenous factors seem to exert a certain influence upon the relative sensitivity of the skin of different individuals to roentgen-rays. Deutschländer; Mühsam; Beck; von Jaksch; and others noted that blonde and fair skinned persons, who do not tan easily, react more readily and vehemently to roentgen-rays than dark pigmented individuals. Similar observations were reported by Voltz with the therapeutic application of roentgen-rays in gynecological cancer cases. The skin of babies and infants is said to be more sensitive than that of adults. Hohlfelder stated that babies up to three months old develop an erythema after the application of only 20 to 25 per cent of the erythema dose for adults; other investigators, however, maintain that these differences are less marked.

An increased sensitivity to roentgen-rays may result from certain endogenous or exogenous conditions such as pregnancy, diabetes, exophthalmic goiter, eczema, psoriasis, Addison's disease, malaria, tuberculosis of the bones and joints, lupus, nephritis, marasmus, or scar tissue (Groedel and Lossen). The same effect may be elicited by the following exogenous agents: pressure; friction and other types of mechanical trauma; ultraviolet rays; various drugs, such as arsenic, mercury, silver, gold, bismuth, iodine, quinine, turpentine, photographic developers, soap; and other chemical agents which may produce an inflammatory or hyperemic reaction in the skin (Kuznitzky and Jacoby; Gutzeit).

The question concerning the existence of an idiosyncrasy toward roentgen-rays, while still controversial, is answered in general in the negative (Gocht;

Hesse; Gutzeit). Such claims (Bordier) may not have considered that the skin does not become increasingly tolerant to roentgen-rays upon continued exposure, but, on the contrary, rapidly more susceptible to their action, which is cumulative (Dohan and Kienböck; Groedel and Lossen).

Constitutional conditions, however, doubtlessly cause variations in individual reactivity to roentgen-rays (Dohan and Kienböck). As an illustration of such individual differences in sensitivity, Fuss cited an observation in connection with the effects produced in three workers engaged in the same type of work under apparently identical conditions. One of these men developed after 6 months of exposure a severe chronic roentgen-dermatitis which ultimately necessitated the amputation of one finger, while the other two technicians showed only minor cutaneous reactions. It may be pointed out that such marked discrepancies in the reactivity of several workers to this or any other occupational carcinogenic agent often are based not so much on constitutional differences, but on variations in working and living habits which sometimes entail considerable differences in the degree of exposure.

XIII. PROGNOSIS

The ultimate prognosis of chronic roentgen- and radium-dermatitis and cancer depends upon various factors (Dible and Morison). It appears to be essential for a good prognosis of chronic roentgen-dermatitis that any further contact with roentgen-rays and radioactive substances shall be eliminated as soon as the first symptoms of a chronic dermatitis are noticed. While there is slight prospect that the changes, once produced, may recede after a prolonged period, they may be kept at least stationary by avoiding any additional contact with the actinic agent. If exposure to the injurious rays ceases early enough, cancer development may not ensue in spite of the presence of burns (Rowntree). Gütig asserted that the timely cessation of exposure may cause a lowering in the degree of malignancy of a tumor which may develop ultimately after a long period of latency (Saunders and Montgomery); Gütig pointed out in this connection that almost all those individuals who continued their professional work after the production of malignant lesions died with a metastasizing carcinoma. The early removal of the precancerous hyperkeratoses and cancers may offer, on the other hand, a relatively fair prognosis, provided that any further contact with the rays is avoided. However, the ultimate prognosis of chronic roentgen-dermatitis and carcinoma remains always uncertain, because of the multiple or even diffuse character of the cutaneous changes, the notoriously long latency period of the malignant manifestations, and the occurrence of late recurrences (Schümann).

In conformity with the factors controlling the ultimate outcome of cancers in general, also that of roentgen-cancers of the skin depends upon their relative tendency to produce metastases in the regionary lymph nodes and in remote organs as well as upon the presence of such secondary deposits at the time

the therapeutic measures are instituted. Roentgen-cancers are in general slow to involve the regionary nodes, that is, in most of the professional cases, the lymph nodes of the cubital and axillary regions. However, metastases into remote organs have been observed repeatedly (Hesse; Krause; and others). Hesse recorded the presence of metastases in 26 per cent of his cases. Flaskamp noted an incidence of metastases in 24 to 26 per cent, while Walischewski stated that in 11 out of 55 cases of occupational roentgen-cancer metastases were found. In Brown's series metastases were recorded in 19 out of 28 cases. The development and spread of the secondary growths is sometimes very sudden and early, and, occasionally, of an explosive character(Hesse). Similar observations were made by Walischewski in 5 of his 55 cases. Roentgen-cancers may display thus a high degree of biological malignancy.

The information concerning the mortality rate of roentgen- and radium-cancers is unreliable. The ultimate fate of many of the recorded cases of these types of occupational cancers is unknown. Hesse noted a mortality rate of 20.3 per cent; Porter of 25 per cent; Rowntree of 23 per cent; Coenen of 24 per cent (including cases of lupus cancer); Gutzeit of 19 to 25 per cent.

XIV. EXPERIMENTAL ROENTGEN- AND RADIUM-CANCER

The first attempts to produce experimentally roentgen-cancer were made by Rowntree (1909), who exposed the tails of rats and the ears of rabbits to one or one and a half erythema doses of roentgen-rays, but obtained only changes characteristic of chronic roentgen-dermatitis (alopecia, hypertrophy of hair follicles and sebaceous glands, fibrosis of the subcutaneous tissue). In the same year Marie, Clunet and Raulot-Lapointe succeeded in obtaining a malignant tumor of spindle cellular structure in the cutis of a rat following repeated application of roentgen-rays for 18 months.

The first actual roentgen-carcinomas were produced by Bloch (1924), who exposed the ears of four rabbits to repeated administrations of roentgen-rays. While two rabbits died early with evidence of chronic roentgen-dermatitis (hyperpigmentations and depigmentations, alopecia, atrophy of skin), two survived and developed carcinomas of the ears after 25 months from the start of the experiment and after an exposure to 1,270 r and 2,000 r given within 13 months and 3 years, respectively. The administration of 888 r to the ear of one of these rabbits elicited only chronic dermatitic reactions. Subsequently, the cancerous ears exhibited complete alopecia 10 months after the start of the treatments and, later, atrophy of the skin; depigmentations; angiectases; diffuse desquamation of a horny membrane, circumscribed, partly follicular, partly verrucous hyperkeratoses. In one of the two rabbits, malignant lesions appeared 13 months after cessation of exposure. The rabbit which received the higher dose and which was irradiated while the cancer was already in existence died four years after the start of the experiment with metastases in the regionary lymph nodes and lungs, whereas the carcinoma produced with the

lower dose remained localized, but invaded by direct extension the contents of the skull. The neoplasms formed in both animals were cornified squamous cell carcinomas displaying a high degree of irregularity in size, shape and stainability of the cells and nuclei. In addition to numerous multinucleated giant cells and giant cells with multiple mitoses, there were protoplasmic keratinizations in nucleated cells, and cellular dysplasia and dyskeratosis in parts of the tumor tissue.

The observations of Bloch were confirmed by Schürch (1930), who exposed the ears of 28 rabbits to roentgen-rays over a prolonged period and studied in detail at certain intervals the histological changes present in the exposed organs, thereby obtaining a rather complete picture of the various developmental phases of chronic roentgen-dermatitis which ultimately ended in malignancy. The time of exposure in these experiments varied from 14 days to 33 months, while the dose administered ranged from 60 r to 3,895 r. The observation time extended from 14 days to 43 months. Cancers of the ears were obtained in three rabbits, which had received a total dose of more than 1,000 r. The tumors became manifest after more than two years from the start of the experiment. The cancers originated in the margins of ulcers and were of a scirrhous type. Metastases were found in the regionary lymph nodes at the base of the ears. In addition to the malignant neoplasms, there developed massive and multiple filiform papillary excrescences near ulcerative perforations or remote from them in the irradiated ears after 27 to 31 months of treatment. The verrucous tumors were partly red and had the appearance of angiokeratomas.

In contrast to the relatively long developmental period apparently needed for causing a carcinomatous response in rabbits, Jonkhoff reported the production of experimental roentgen-cancers in the skin of mice after a minimum latency period of one and a half months (maximum latency period, 10 months, or nine months after the last exposure to the rays). Three treatments were given per week until a total of 14 treatments was administered. Of the 6 mice thus treated, four developed malignant tumors (3 spindle cellular sarcomatoid carcinomas, 1 squamous cell carcinoma) originating in the edges of ulcers and growing into massive proliferations. Pulmonary metastases were found in one mouse. Jorstad and Lane produced roentgen-burns in rats and observed folliculo-epitheliomas after 8 months, following a thinning of the epidermis appearing after 30 days of the treatment, and after a hyalinization of the subcutaneous connective tissue associated with the development of mild hyperkeratoses and marked epidermal thinning had become evident 60 to 90 days later.

The experimental production of carcinoma of the skin in animals by the action of radioactive substances has been accomplished in more recent years. Daels and Baeten obtained a cornified squamous cell carcinoma in a mouse 322 days after the implantation of a seed filled with several drops of a solution

containing 10 mgm. of radium bromide in 100 cc. of water. A cutaneous carcinoma in a mouse was produced by Barlow by an exposure to radium sulfate. The occurrence of two squamous cell carcinomas in the skin of rabbits following the implantation of radium in platinum tubes into the subcutaneous tissue was recorded by Ross. This investigator mentioned that one of the tumors contained a stroma plentifully supplied with thin-walled vessels and infiltrated with eosinophilic cells. One of the two neoplasms produced metastases into the lymph nodes and lungs.

XV. CAUSATIVE MECHANISM

The causative factor or factors active in the production of roentgen- and radium-cancers and the mechanism through which they bring about, directly or indirectly, a malignant cellular change in the epithelial cells of the skin are still matters of speculation and surmise. It is even uncertain whether the radiating energy causes such an effect by acting directly as a physical agent upon some component part of the cell or of the organism; or whether the penetrating, non-corpuscular waves elicit chemical changes, which, in turn, elicit cellular reactions responsible for the cancerization of the cells. It is unknown also whether such hypothetical chemical changes are of specific or of nonspecific nature, that is, whether carcinogenic substances of definite types or merely general irritative agents are produced. Nevertheless, a number of theories concerning the causation of these carcinomas have been advanced, which are cited here and analyzed for their respective merits.

The hypothesis of Cohnheim does not seem to be applicable regarding the carcinogenesis of roentgen-tumors, as it cannot be assumed with any degree of justification that the multiple precancerous and cancerous lesions observed in the roentgen-skin represent foci of misplaced embryonic cells activated into an increased proliferative activity by the action of the rays. Similar objections must be raised against the application of Ribbert's theory, because it is even less probable that localized germinative tissue anomalies, which presumably are not demonstrable by morphological methods, are stimulated into a malignant growth by the actinic agent. The histological findings in chronic roentgen- and radium-dermatitis provide also little, if any, support for the supposition of Ribbert that cancer originates from cells excluded from their normal cellular contacts (Flaskamp and Wintz).

The theory of Virchow that chronic irritation is the cause of cancer has a good number of supporters in connection with the genesis of these actinic neoplasms. The roentgen-cancer has been acclaimed as a typical example of this type of carcinogenesis. Apart from the fact that the general significance and value of this theory has diminished greatly since the discovery of specific carcinogenic agents, roentgen-dermatoses of chronic nature, when uncomplicated by secondary infections, are not characterized by a great deal of inflammatory reactions. Bloch remarked that the concept of irritation in con-

nection with the carcinogenesis by roentgen-rays is not only vague, but that it is also insufficient even in the presence of an individual predisposition for a cancerous response. The quality of the "irritative" action is the important part for Bloch. Béclère noted that the theory of non-specific chronic irritation as the cause of roentgen-cancer was not any more convincing than it was in relation to cancer in general. Schürch concluded that the roentgen-cancers do not develop simply on the basis of a chronically injured skin, but follow upon the appearance of special developmental conditions brought about in the tissues by the rays. Similar negative opinions in this matter were expressed by Flaskamp and Wintz.

Wyss (1906, 1908) proposed an ischemic theory of roentgen-carcinogenesis. This investigator pointed out that the circulatory disturbances, produced in the irradiated skin by the intimal proliferative and medial hyalinizing processes in the cutaneous vessels and by the production of scar tissue, result in an insufficient nutrition of the epidermal cells, which by such changes are more or less excluded from the union with the body and therefore assume an independent existence as cancer cells.

A similar conception was advanced by Wolbach, who contended on the basis of his own histological observations and those of Wyss and Unna, that the epidermis is the least radio-sensitive part of the skin, and that any neoplastic reactions originating in the epidermis are secondary to and conditioned by the primary progressive degenerative lesions of the vasculo-connective tissue causing an interference in the blood supply reaching the epidermis. It was claimed by Wolbach that the epithelium preserves its normal reparative and proliferative ability, and that the gradual acquisition of malignant qualities by these cells is attributable to a constant excessive demand for regeneration. Ledoux-Lebard expressed a similar opinion concerning the cancerizing effect exerted upon the epidermis by the pathological changes in the connective tissue produced by the rays. The reasoning of Wolbach is accepted apparently also by Cole, who stated that the malignant changes in roentgen-skin resulted from the efforts of the epidermal cells proliferating infiltratively into the corium in search for adequate nourishment and becoming parasitic in the end. A prolonged nutritional deficiency of the epidermis caused by the sclerosis of the corium was incriminated by Daels and Baeten for the production of biologically modified epithelial cells which finally assume lytic qualities enabling an invasive growth.

Upon close inspection it is evident that the theories advanced by Wyss, Wolbach and others are the morphological equivalents of the biochemical theory of cancerigenesis proposed more recently by Warburg. However, this anoxemic theory of malignancy has been shown to be unsound not only from a biochemical standpoint, but also from a morphological one. Hesse pointed out in 1911 that the great majority of investigators had abandoned the conception that the primary damage done by the roentgen-rays was exerted on

the vasculo-connective tissue of the skin, and were conceding a direct destructive action of the radiating energy upon the epithelium. It may be mentioned that Unna's observations and interpretations of the histological changes in chronic roentgen-dermatitis do not support Wolbach's viewpoint, as Unna emphasized the fact that in chronic radiodermatitis no deep and extensive vascular injury existed.

Rosenbach, on the other hand, pointed out that the cutaneous tissues from which roentgen-cancers originated were well vascularized. He argued that inasmuch as the epithelial cells received the direct and most intense effect of the rays, while the action of the rays upon the underlying connective tissue was somewhat weakened, this factor accounted in part for the frequency of roentgen-carcinomas and the relative rarity of roentgen-sarcomas of the skin. The scarcity of the sarcomatous neoplasms did not indicate in the opinion of Rosenbach the existence of any natural inertness of the connective tissue to the cancerigenic action of the rays. It may be mentioned that experimental observations on the production of roentgen-sarcoma made in more recent years confirmed this part of Rosenbach's argument.

Schümann, who showed that there did not exist any interference with the circulation in the skin with chronic radiodermatitis, and that, quite to the contrary, an abundance of capillaries and larger vessels was present in and around roentgen-cancers, noted that it was not feasible to explain the development of these neoplasms on the production of primary obliterative vascular lesions. A similar opinion in this matter was expressed by Ribbert, who emphasized, moreover, that only healthy cells and not undernourished, degenerated cells were capable of a persistent proliferation such as exists in malignant growths.

In a theory more recently advanced by Handley the main weight of responsibility is shifted from the obstructive processes in the blood vessels to similar changes in the lymphatics. This investigator claims that the main characteristic of radiodermatitis is a proliferative lymph-angitis of the cutaneous lymphatics produced directly or indirectly by the radiating energy and leading to the more or less complete obstruction of these vessels. These lymphatic alterations provide, in the opinion of Handley, the main causative mechanism for the subsequent epithelial changes, which are said to occur in the following sequence and manner: When a capillary lymphatic is blocked the papilla swells up because of the failure of the blocked lymphatic to carry off the fluid which is transuding into the tissues of the papilla from the blood vessels; the papilla elongates and broadens for this reason, and its connective tissue and overlying epithelium receives a nutritional proliferative stimulus which results in the formation of a papillary hypertrophy or wart. This conception limits itself to explaining the developmental mechanism of the precancerous epithelial lesions present in the roentgen-skin without attempting

to formulate any idea concerning the cause of their ultimate cancerization. The observations of Handley concerning the presence of obliterated lymphatics were not confirmed by other investigators, who found these channels in general patent, unless they were compressed secondarily by the formation of scar tissue in the roentgen-skin (Wood). It is not probable that chronic lymphedema has any direct relation to the cancerization process, as elephantiasis of the skin, while causing a hyperplasia of the epidermis at times and occasionally even papillomas and warty growths, does not result in malignant lesions.

Béclère considered the roentgen-cancer as a unique accident in the course of various nonspecific lesions, that is, a complication superimposed upon the ordinary actual roentgen-injury through the action of an unknown, new factor, unrelated to the radiating energy (Regaud). Béclère advanced these arguments in support of his conception: 1) Only a small percentage of radiologists exposed to repeated irradiations develops lesions on hands and fingers; 2) there is no parallelism between the degree of roentgen-injury and the development of cancer; 3) a cancer may develop in a skin which appears to be almost intact, while sparing a skin with very extensive and severe lesions; 4) the histological changes are in most instances not of inflammatory nature, but carry more often the character of neurotropic disturbances; 5) the cancer develops in a more or less atrophic skin with lowered vitality, such as represented by a wart. Some of the arguments used by Béclère in support of his theory are evidently of controversial nature, while others are of little intrinsic value.

A number of investigators favor the view that roentgen- and radium-rays produce malignant growths by causing the development of a cellular mutation elicited through a direct action of the radiating energy upon some molecular constituent of the chromosomes (Bauer). This conception receives much support by the well established fact that cellular mutations of various types follow upon the exposure of embryonal cells to these physical agents. The occurrence of abnormal, irregular and multipolar mitoses in irradiated cells has been cited as evidence confirming such a viewpoint. It may be pointed out upon examination of this argument that identical chromosomic disturbances are observed in connection with the action of numerous and diverse cellulotoxic agents, which never give rise to the formation of cancerous growths. The occurrence of a direct carcinomatous mutation as a primary effect of the rays appears to be improbable because of the fact that such an event should not necessitate a more or less prolonged action of the rays associated with a long latency period, but should take place at least occasionally after a short and single exposure to these rays, such as present during fluoroscopic examination, accompanied by an early and rapid neoplastic response. Inasmuch as such observations are entirely lacking in the clinical

as well as experimental field, and as roentgen- and radium-cancers in practically all respects behave like chemically induced tumors, the physical mutation theory is in distinct need of pertinent and convincing evidence.

There remains the possibility that roentgen-rays and rays from radioactive substances may elicit specific or nonspecific, primary or secondary chemical changes in the irradiated cells and their component substances which are responsible for the carcinogenic manifestations. Luther noted that roentgen-rays do not produce toxic substances in pharmacologically effective amounts in the cells. This fact, however, does not exclude the possibility that physico-chemical effects brought about by the radiant energy in some of the chemically important catalytic and enzymatic components of the cells may exert a fundamental action upon the reactivity and vitality of the affected cells (Dessauer; Hardy; Spiegel-Adolf; Waterman; Loew-Beer and Reis; Gottschalk and Nonnenbruch; Heeren and Pansdorf; Hueper; and others). While thus a certain amount of circumstantial evidence seems to support such a conception, at the present time it remains chiefly speculative.

Finally, mention may be made of the theory of Bordier, who contended that the radiant energy gradually elicits a sort of allergic condition of the skin, on the basis of which the papillomatous hyperkeratoses, developing as the result, become ultimately transformed into epitheliomas. It does not appear likely from the evidence available that such a development is related to the existence of a physical hypersensitivity, because hyperplastic and neoplastic lesions often appear in the roentgen-skin many years after the cessation of exposure.

XVI. THERAPY

The therapy of the roentgen- and radium-cancers begins with the early and proper treatment of the precancerous cutaneous manifestations, especially keratoses and ulcers, so as to forestall the subsequent development of the malignant sequelae. Various soothing and bland ointments, lotions and pastes are used in the management of the congestive and inflammatory reactions with and without exudation which are associated with acute radiodermatitis (Cole; MacKee). Indolent roentgen-ulcers have been treated at times successfully with applications of fresh leaves of aloe vera (Collins and Collins; Wright); or with exposures to solar or ultraviolet rays; or by surgical excision, where necessary, followed by skin grafting.

The hyperkeratotic warty lesions characterizing chronic radiodermatitis may be removed by deep fulguration, by cautery or electrodesiccation (Saunders and Montgomery; Pfahler; Eller; Béclère) or by the use of carbon-dioxide snow (Cole). The employment of ultraviolet light in the treatment of chronic radiodermatitis is recommended by Cole; Lassar; Holzknecht; and others, but is considered to be of questionable value by Saunders and Montgomery; Eller; Blair; Bordier; Davis; and Soret. Bordier reported beneficial results from the use of diathermy. The replacement of the injured

skin by full skin grafts is not only the most efficient method of treatment of chronic radiodermatitis, but also the safest one, as it eliminates any possibility of a subsequent malignant development (Porter; Béclère; Davis; Saunders and Montgomery). In cases in which such radical procedures cannot be taken, care should be exercised to avoid not only further contact with the radiant agents, but also exposure to agents which may irritate the skin [reducing chemicals (ichthyol), photographic fixatives and developers, ether, or mercury bichloride (Dohan and Kienböck)] as such cutaneous hyperemia producing substances may cause the development of an eczema and may stimulate the proliferative processes present in the skin, thereby counteracting the effect of therapeutic measures taken.

Whenever there appears a suspicious lesion, biopsies should be taken so as to determine its actual biologic nature and to institute thereupon the proper therapeutic steps (Saunders and Montgomery). However, it must be pointed out that the information obtained from biopsy specimens may be misleading, as the cancerous part of larger lesions may be small and, therefore, may be missed at the removal of the tissue (Hesse). It is advisable to prepare roentgenograms in all cases in which suspicious lesions are located near bony structures, as osseous involvements may exist at a time when relatively minor subjective symptoms are encountered. The physical examination of individuals with roentgen-cancers should include always an inspection and palpation of the regions containing the proximal lymph nodes before any therapeutic procedures are undertaken. Surgical removal of malignant manifestations offer apparently the best curative chances, especially as long as the neoplasm is localized. It is essential, however, that the operative procedures are of sufficiently radical nature and are taken early, before metastases have occurred, as many a case of roentgen-cancer has been lost in the past by piecemeal surgery (Handley) and by temporizing in order to save a digit or an extremity (Saunders and Montgomery).

The treatment of roentgen- and radium-cancers with roentgen-rays or radium has been recommended by Roffo, but the rationality of this therapy must be doubted considering that the radiating energy applied for the destruction of the malignant lesion may provide a sufficient stimulus for the conversion of adjacent precancerous changes into definitely malignant ones. Ullmann noted that the use of roentgen-rays for such purposes produces a temporary destruction of the sensitized tissue which, however, is followed by a severe lethal recurrence.

XVII. PREVENTIVE, PROTECTIVE AND SANITARY ASPECTS

The occurrence of an appreciable number of occupational and therapeutic roentgen- and radium-cancers of the skin as well as of several other types of serious actinic injuries (acute and chronic dermatitis, atrophy of testes and ovaries, leukopenia, anemia, leukemia, osteogenic sarcomas, and pulmonary

carcinomas) was the reason for the introduction and elaboration of certain precautionary and sanitary measures intended for the protection of the individuals coming in occupational contact with these injurious physical agents. Scientific bodies from many countries cooperated in drawing up rules and regulations to be observed by the personnel of roentgen- and radium-laboratories of all types, to govern the construction, installation and operation of roentgen-equipment as well as the production and handling of radioactive substances. These recommendations have been elaborated and modified from time to time [Advisory Committee on X-ray and Radium Protection, U.S.A. (Taylor); Safety Committee, American Roentgen-Ray Society; British X-ray and Radium Protection Committee (composed of Royal Society of Medicine; Roentgen Society; British Association for the Advancement of Radiology and Physiotherapy; Institute of Physics; Radium Institute; National Physical Laboratory); Deutsche Röntgengesellschaft; etc. (Riegele; Brandt and Lange; Laborde and Leclercq; etc.)].

These three conditions must be fulfilled to accomplish complete protection of operators of roentgen-apparatus (Riedel): (*1*) The emission of roentgen-rays laterally and backward from the beam must be prevented; (*2*) the secondary and scattered-rays must be made innocuous; (*3*) the rays which have penetrated the body of the patient must be arrested before they contact the operating and examining individuals. The first condition is practically fulfilled since the introduction of self-protected tubes. The fulfillment of the second condition has proved to be more difficult and little has been accomplished so far in this respect. The third condition has been fulfilled only partially by interposing a special type of protective lead glass screen between the patient and the examining person during the performance of fluoroscopic examinations.

The escape of penetrating roentgen-rays from the roentgen-room into adjoining quarters entailing a hazard for individuals living or working there can be prevented effectively by lining the walls, floors, ceiling, and doors with lead sheets of proper thickness (depending upon the hardness of the rays produced). Care must be taken to overlap the edges of the sheets so as to stop any leakage through crevices. Adequate protection can be obtained also by the use of bricks containing Portland cement (one part), barium flour (2 parts) and barium sulfate (one part), which must be properly grooved and tongued to prevent leakage at the joints.

The evidence available indicates that satisfactory working conditions require that a person in normal health should not be exposed to a dose exceeding about one roentgen of roentgen-rays or gamma-rays per week, or in one year of 300 working days a dose of not more than 60 r. Medical examinations of roentgen-personnel, giving special emphasis to the condition of the blood, should be made at intervals of not less than six months. The annual vacation period should be no less than four weeks.

Similar protective measures have been devised concerning the handling of radioactive substances. However, complete protection against the highly penetrating gamma-rays is difficult to obtain when handling radioactive substances (Hunter; Laborde and Leclercq).

XVIII. MEDICO-LEGAL ASPECTS

Roentgen- and radium-dermatitis and cancer are among the compensable occupational diseases in most countries [Argentina, Australia, Belgium, Bulgaria, Cuba, Finland, Germany, Great Britain, France, Ireland, Mexico, Norway, Peru, Portugal, Rumania, Sweden, Russia, United States (Carozzi; Laborde and Leclercq)].

The compensation laws in force in the different countries cover in part the specific diseases, in part the causative agents and operations, and in part either two or three of these factors. In most instances the law provides for a maximum period of responsibility, so the extent of protection afforded by the law rests to a certain extent within this clause. In France, for instance, for acute and chronic radium-dermatitis the law permits a delay period of up to one year, that is, within one year after the cessation of the hazardous work which caused the injury, claims must be made. For radium-cancer the delay period is five years. Similarly objectionable laws have been enacted in other countries (International Labour Conference; Laborde and Leclercq; Carozzi). The delay periods are obviously too short to cover an appreciable number of cases. Such limitation clauses entirely disregard the biological character of the disease which the laws are supposed to cover.

In as much as roentgen- and radium-cancers are still serious occupational diseases that must be reckoned with in the future, Groedel and Lossen proposed to place all establishments using radiating energy produced by roentgen-tubes or radioactive substances under the direct supervision of governmental agencies which should be charged with the task of enforcing the installation and observation of adequate technical and medical precautionary measures in these laboratories.

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B. Physical Trauma—Benign Pseudotumors

a. Traumatic Epithelial Cysts

Traumatic benign epithelial cystic formations located in the subepidermal and subcutaneous tissue appear in the literature under various names, such as kyste épidermique, kyste dermoides, acanthoma adenoides cysticum, epithelioma adenoides cysticum, epidermoid implantation cyst, etc. They have been mistaken for epithelial cystic formations of different origin, such as atheromas and keratomas of sebaceous glandular and ductal genesis, and congenital epidermoids and dermoids, with which they have certain macroscopical and microscopical similarities.

Their present generally accepted name of traumatic epithelial cysts was introduced by Garré after Gros as well as Reverdin had pointed out that these epithelial cavitations, usually located on the volar surfaces of the hands and fingers, were not peculiarly situated atheromas, but were of traumatic origin. It must be mentioned, however, that such a genesis is not demonstrable for an appreciable proportion of the reported cases of epithelial cysts of this site. Wörz found in only 24 out of 55 cases of this type adequate evidence of a preceding trauma, while Pietzner demonstrated such a relation in 43 out of 73 cases. Nevertheless, a considerable number of well authenticated cases of traumatic epithelial cysts has been placed on record (Buerger; Blond; Pietzner; Garré; Gros; Reverdin; Wörz; Kummer; Sutton; Bissel and Brun-

schwig; Harris; Behrens; Curtis and Owen; Burrows; Blumberg; Franke; Hammann; Parns; Avoni; Carossini; Sheck; Beust; Maron; Ivavenko; Critehett and Griffith; Sauerbruch; Sonntag; Friedländer; Dreyfuss; King; Wien and Caro; Hartley; Pels-Leusden; Woringer and Marques; Nürmberger; Vincent; Cogswell and Goodale; and others.

I. OCCUPATIONAL RELATIONS

Traumatic epithelial cysts are especially common in shoemakers, cobblers, carpenters, tailors, manual laborers, and mechanics, that is, in workers who are exposed by their particular occupational activity to traumatization of the fingers and hands (Hartley; Wien and Caro).

II. INCIDENCE

Garré reported in 1894 a total of 37 cases of traumatic epithelial cysts collected from the literature. Wörz increased this number in 1897 to 58 cases, of which in his opinion, however, only 24 had an adequate traumatic history. Pfietzner was able to collect an additional 75 cases of epithelial cysts, of which 43 showed a traumatic history. Parns added in 1914 twenty-five new cases, and Hammann stated in 1930 that since that time 37 additional cases had been placed on record. This number was increased by the end of 1939 by approximately 40 new cases, to which Cogswell and Goodale added in 1940 37 cases, making a total of 270 cases of epithelial cysts, the majority of which possess a definitely traumatic origin.

A recent report of Nürmberger who observed 17 traumatic epithelial cysts in a series of 178 cystic epithelial tumors of the skin, of which 121 were epidermoids and 40 were dermoids, furnished some information concerning the relative incidence of the traumatic epithelial cystic formations.

III. TYPE OF TRAUMA

The injuring force may be dull (blow, fall, or contusion) or sharp (perforation by cut, stab, tear [knife, wire, splinter, needle, fork, nail, or by some other sharp instrument]). It is not infrequently associated with an injury to the nail of the finger (splitting, perforation, tearing), but is not always accompanied by a break in the skin. The trauma is followed sometimes by a suppurative process.

IV. SITE

The great majority of the traumatic epithelial cysts are situated on the volar surface of the fingers, especially of the distal phalanx (about 75 to 80 per cent). A smaller number is located on the palm of the hands (Garré; Wörz), a few of the cysts are found on the dorsal side of the fingers, while other sites are exceptional (toe [Wörz]; dorsum of foot [Wien and Caro]; forehead [Hartley; Bland-Sutton]; forearm, neck, cheek, orbital region, forehead, buttocks, leg [Cogswell and Goodale]). The cysts are most often

embedded in the subcutaneous tissue. In several instances, however, the cysts were present within the bone of the terminal phalanx (Bissel and Brunschwig, 2 cases; Behrens, 2 cases; Friedländer, Harris, Sonntag, Hammann, Burrows, Dreyfuss, Curtis and Owen, 1 case each). In a few cases they were located in the frontal bone of the skull (Hartley; Sauerbruch) or within the orbit (Critehett and Griffith). There were, in addition, several cases in which the cysts had produced, through pressure atrophy, a cavitation in the cortex of the phalangeal bone.

It may be pointed out in this connection that sebaceous gland cysts involve, as a rule, most often the haired parts of the head (Caylor), while dermoids prefer the regions of the embryonic fissures of the head and spinal column (Hartley).

V. LATENCY PERIOD

The latency period, that is, the time which elapses between the traumatic incident and the appearance of the first evidence of a cystic formation in the injured area, varies greatly with the individual case. The range is from 1 month to 24 years (Bürger). Inasmuch as these cysts exhibit a very slow growth, usually many more months or years pass before the symptoms become sufficiently severe to call for a therapeutic measure.

VI. AGE

Conforming with the etiology and slow developmental course of these conditions, the age of the individuals affected is usually the adult period, less often, adolescence, and rarely, childhood (Bürger). King gave the age range as from 10 to 70 years, adding that it is the exception when a case is observed in a person less than ten years old. The following table presents the age distribution of 20 cases collected from the literature.

AGE DISTRIBUTION OF TRAUMATIC EPITHELIAL CYSTS

Years	10–20	21–30	31–40	41–50	51–60	Total
Cases	5	2	5	6	2	20

Sex. The traumatic origin of the epithelial cysts is reflected in the sex ratio, which is approximately 1:5 in favor of the male sex (18 females to 90 males).

VII. SYMPTOMATOLOGY

The first symptoms are a gradually increasing swelling and tenderness, which is often experienced only on pressure. The nodular, cystic, well circumscribed, rounded formation measuring usually 1 to 2 cm. in diameter, rarely more, may be adherent to the skin or to the underlying tissue. The tumor may vary in size from a split-pea to a walnut. The roentgen-examination of the involved part may show a superficial erosion of the bone or, with intraosseous lesions, a sharply outlined cavitation of a swollen bony structure with rarefac-

tion of the surrounding bone (Harris; Bissell and Brunschwig). Upon surgical enucleation, superficial lesions appear to be surrounded by a well developed fibrous capsule, which is lined on the inside either entirely or partially by a smooth, white membrane. Granular tissue may cover the remainder of the cystic wall. A serous, viscous material or a cheesy, scaly or lamellated, horny matter form the content of the traumatic epithelial cysts.

VIII. HISTOLOGY

A fibrous capsule is lined by a stratified and cornified squamous epithelium which in turn is covered by a laminated keratin. There are no glandular organs or hair follicles included in the epithelial coating in contrast to the anatomical composition of sebaceous gland cysts and dermoids. Parts of the cystic wall may be composed of a chronic inflammatory granulation tissue containing foreign body giant cells.

IX. CAUSATIVE MECHANISM

The traumatic origin of these formations is based upon the circumstantial evidence presented by the traumatic history, the peculiar local distribution, the preference for certain occupations, the age distribution and the histological structure. The traumatic causation of these lesions is supported by the results of experimental subcutaneous implantations of epidermis into the subcutaneous tissue of animals. Kauffmann implanted pieces of the epidermis into the subcutaneous tissue of the combs of roosters and chickens, and obtained epithelial cysts surrounded by a granulation tissue containing giant cells. Similar results were reported by Ribbert, who produced epithelial cysts in the subcutaneous tissue of rabbits by epidermal implants. Manasse and Schweniger, who made similar experiments, emphasized that the implanted epidermis did not need to be connected with blood vessels to remain vital and for forming the epithelial cysts. Peer and Paddock observed that cystic cavities, lined by epidermis and containing horny material and fragments of hairs, appeared in deeply implanted dermal grafts. While the sebaceous glands, hair follicles and sweat glands regressed in the grafted tissue after some time, the epidermal tissue was surrounded at the same time by a granulation tissue containing foreign body giant cells, epithelioid cells, etc. Epidermal cysts were produced in rats by the transplantation of skin flaps beneath the skin (Burckhardt and Müller).

Whereas these observations support the traumatic implantation theory of the genesis of traumatic epithelial cysts, Pels-Leusden offered experimental evidence suggesting that these cysts may originate from the epithelization of traumatic subcutaneous cavities formed by a liquefaction necrosis from the proliferating epithelium of the epidermal appendiceal organs. This investigator placed small magnesium plates under the skin of rabbits and found that an epidermization of the cystic cavity formed around the foreign body

originating from the proliferation of the adjacent glandular epithelium. It may be mentioned that a similar mechanism is apparently active in the formation of the epidermal cysts seen after the subcutaneous injection of scarlet oil into the ears of rabbits. The probability of a genesis of epithelial cysts from the surface epithelium, on the other hand, is suggested by the processes leading to the epithelization of osteomyelitic sinuses, of the cavity of the middle ear following perforations of the ear drum (leading sometimes to the formation of cholesteatomas) (Kelemen), of traumatic dentigerous cysts of the jaw (Blum; Morehead and Dewey), and by the development of epithelial cysts in the iris of the eye, following perforating injuries to the eyeball (Bonnet and Paufique; Moore).

X. MALIGNANT POTENTIALITY

Accidentally or experimentally produced epithelial cysts of the epidermis represent excellent evidence contradicting the dogma of Ribbert that traumatically misplaced epidermis may form a predisposed anlage for carcinogenesis. It is a well established fact that these traumatic epithelial lesions exhibit almost no cancerigenic tendencies (Teutschlaender), in spite of the statement of Ewing that many become malignant. There is only a single case on record for which a secondary cancerization is claimed (Franke). A cornified squamous cell carcinoma was found in this particular epithelial cyst occupying about one half of its circumference.

Attempts which were made to bring about a malignant transformation of the epithelial lining of experimentally produced cysts by causing an additional irritation through the intracystic injection of normal saline, olive oil, distilled water, 10 per cent sodium chloride solution, scarlet red and tar, made 2 to 3 times weekly, succeeded only in stimulating a transitory growth of the cyst with the production of peculiar cystic, endotheliomatoid formations in the surrounding tissue, while the epithelial lining remained without any appreciable proliferative activity (Burckhardt).

The refractory behaviour of traumatic epithelial cysts toward a secondary cancerization is in strong contrast to the malignant tendencies displayed by sebaceous gland cysts which have their favorite localization in the skin of the scalp, face, back and scrotum (Seff and Berkowitz; Caylor). In a series of 236 sebaceous gland cysts observed by Caylor, 12 were cancerous (3.44 per cent). The majority showed squamous cell carcinomas, a few were of the basal cell type. Bishop studied 119 sebaceous gland cysts and keratomas (firm, solid tumors with a lamellated structure arising from the epithelial lining of the sebaceous ducts) and found 11 carcinomatous and 2 precancerous lesions (9.2 per cent). Stone reported an incidence of 2.2 per cent of malignant transformations in his series of sebaceous cysts. A total of 87 cases of carcinomas originating in sebaceous gland cysts was collected from the literature by Collins. It is remarkable in this connection that keratomas seem to be devoid

of any malignant tendencies (Bishop), while the sebaceous gland cysts which contain the decomposing sebum, consisting in part of cholesterol esters, show an increasing incidence of malignant transformation parallel to the age of the cyst and of the individual. Bishop noted that a causal influence of this type upon this process of malignant transformation seemed to be present in two of his cases in which cancer developed in a sebaceous gland cyst. While carcinomas originating in sebaceous gland cysts rarely form metastases, they recur frequently after attempted removal.

Malignant Neoplasms—Traumatic Carcinomas of the Skin. While the majority of the occupational carcinomas of the skin (79 to 97 per cent) originate on the basis of more or less diffuse cutaneous changes and in areas most intensely exposed to the different specific carcinogenic exogenous agents (face, neck, hands, scrotum) (Naegeli), accidental, traumatic epitheliomas exhibit a definite relation to locally restricted areas, which are determined by the more or less fortuitous action of a mechanical trauma causing nonspecific circumscribed structural and physico-chemical tissue changes.

The claims advanced concerning the allegedly traumatic causation of cutaneous carcinomas vary greatly with different investigators. It is safe, however, to disregard all those contentions which note a relatively frequent causal relation between an accidental injury to the skin and a subsequent malignant development. The assertion of Röpke, for instance, that 11.3 per cent of 1,248 cases of skin cancer were attributable to a previous single trauma, belongs to this group. Similarly, Hauser's statement that among 104 skin cancers, 12 cases showed a definite traumatic relationship, whereas in 21 cases such a causal connection was possible, seems to be based on an indiscriminate evaluation of the historical data furnished by the patients. This aspect of the "traumatic" etiology of skin cancers was emphasized especially by Körbler who reported that such claims were advanced by the patients in 45 or 17.4 per cent of 259 cancers of the nose, and in 36 or 15.8 per cent of 243 carcinomas of the face. Körbler remarked that actually trauma played only a minor role in the development of these tumors as the information offered by the patients was considered unreliable.

With due regard for these exaggerated claims there are, nevertheless, a limited number of cutaneous epitheliomas on record in which a mechanical trauma appears to have played a major and decisive role in bringing about the neoplastic reaction. While little divergence of opinion exists as to the actuality of an occasional malignant transformation of a chronic traumatic cutaneous ulcer, many competent investigators deny categorically that a malignant epithelial growth may develop within a few weeks following a single traumatization (acute traumatic epithelioma) as the result of the injury sustained (Barkmeyer; Knox; Ewing; Körbler; and others).

It is difficult to conceive in the light of information available concerning causative factors active in producing cancerous proliferations that a solitary

traumatic incident, affecting a previously intact and normal skin, should result in the rapid development of such a lesion. Such an outcome, however, is entirely in the domain of possibility, if the trauma involves a predisposed skin in which the injurious effect merely precipitates the onset of a long prepared proliferative phase in a neoplastic anlage that is so far quiescent. Such a potentially cancerous focus is not necessarily represented by a congenital disturbance of the skin, but more likely may be a product acquired by a post-embryonal exposure to some of the many exogenous carcinogenic agents. Such a conception would place the traumatic episode at the end of a chain of events in which the accidental injury, possibly, plays an important, but not always an essential role in the development of the neoplasm. This conclusion is supported by the facts that a great many so-called traumatic epitheliomata of the skin are situated in those parts which are normally exposed to solar radiation on the one hand, and that there is an insignificant numerical relation between industrial scars and cutaneous malignancy on the other hand. While physical injury thus does not belong to the specific auxetic agents, it may operate as a provocative factor of a cancerous growth in a predisposed soil, thereby establishing a relationship between trauma and epithelioma, recognized as an undeniable fact by several experienced investigators (Wainwright; Mason; Hickel and Oberling; Leighton and Schmidtke).

Hauser considered the following three possibilities of a causal interrelation between trauma and skin cancer: 1) the trauma involves an area in which a tumor anlage exists and activates its potentialities; 2) the trauma acts upon an organism which possesses a generalized neoplastic predisposition and thus determines merely the site of the neoplastic development; 3) the trauma produces a wound and the tumor is formed on the basis of a disturbed healing process. The first two possibilities would be evidently active in the production of acute traumatic epitheliomas, whereas the last possibility would be operative in the development of chronic traumatic carcinomas.

b. General Traumatic Carcinomas

It seems to be characteristic of most cases of cutaneous cancer with an alleged causation by a single trauma that the wound produced showed little or no tendency to heal and that there was a gradual transition from a simple ulcer into a carcinomatous sore (König and Sassen; Ewing; Bang; and others). In cases in which a chronic ulceration developed in the initial traumatic defect, which, in turn, ultimately became malignant, secondary factors, such as infections and therapeutic agents are superimposed upon the primary traumatic effect and complicate the situation concerning the etiological role played by the trauma in the production of the cancer (Mason). A great variety of injuries and causative agents have been incriminated in the production of traumatic epithelioma (bites by animals, blows, gun shot wounds, puncture wounds [caused by wires, nails, thorns, wood splinters, or metal fragments],

abrasions, lacerations, or contusions) (König and Sassen; Hickel and Oberling; Duhot, Loygue and Delacourt; Lisa and Levine; Duvoir and Abecassis; Lemaitre, Nuytten and Dancourt; Bang; Scheid; Moran; Sweitzer; and others).

It is remarkable that in a series of 37 cases of cutaneous malignancy appearing after a single trauma, 31 tumors were located on the hands, fingers or toes (12 back of hand, 19 fingers or toes), while four involved the face (forehead, temple, nose), one the chest and one the scrotum. In 18 cases of this type, the malignancy started in an injured and subsequently chronically inflamed nailbed (paronychia) affecting especially frequently the index finger, the thumb of the right hand, and the large and small toe, that is, those parts most often subjected to mechanical injuries (Lisa and Levine; Silverman). The latency period varied from a few weeks or months to several years (6 to 20) in these cases. Leighton and Schmidtke, who analyzed recently a series of 79 cases of cutaneous carcinoma following a single injury, stated that 73 of the patients were from 40 to 80 years old when the trauma was sustained, and that in 31 cases the cancers appeared from one to ten months after the injury, and in forty-two others in less than three years. In the majority, the original lesion failed to heal and occasionally involved sites where carcinomas are rarely found (penis: 7 cases). Schrek, reporting his studies of 1,527 basal cell carcinomas and of 1,053 epidermoid cancers, noted that 2.8 per cent of these lesions developed on the basis of scars. The percentage of "scar tumors" was especially high among cancers situated on the legs (44 per cent), scalp (17 per cent), arm (13 per cent) and trunk (9 per cent). The cause of the scarring was extensive burns, roentgen-ray burns, lacerations and surgical operations. In some cases a single trauma was followed by the development of carcinoma. The latency period extended up to forty years. Schrek concluded that scarred skin is apparently more susceptible to the development of cutaneous carcinoma than normal skin, and that the injury itself does not exert a blastogenic action. While Fischer-Wasels asserted that a latency period as short as 2 to 4 months indicated that the trauma activated a preformed cancer, Ewing refused to recognize any causal relationship when the latency period is more than one year. In view of the various additional factors that evidently operate to bring about a malignant response in the presence of a traumatic influence, it is inadvisable to lay down any fixed rules as to the permissible length of the latency period. Whereas a few of the reported cases of acute or chronic traumatic epithelioma of the skin affected rather young individuals (the youngest being 27 years old), the great majority were found in older persons (50 to 78 years old), suggesting thereby that not congenital predisposing factors, but acquired influences are of importance in the genesis of these lesions. The tumors were, as a rule, squamous cell carcinomas; only two neoplasms, located in the face, were basal cell cancers.

c. Special Traumatic Carcinomas

1. CALLOSITIES

There exists a considerable amount of evidence indicating that the keratodermic thickenings of the skin, known as callus and clavus, situated mainly in the palmar surface of the hands and fingers and the plantar as well as dorsal aspects of the toes and foot, are very rarely the source of cancer, if they result from the prolonged and repeated traumatization caused by pressure and friction (Mason), while they give rise to epitheliomas when they are manifestations of a chronic arsenicosis. Callosities of the traumatic type are very common lesions of occupational and nonoccupational origin. The nonoccupational calluses are located usually on the feet and are due to pressure of ill-fitting shoes. The occupational callosities are found most often on the hands and fingers, and result from the pressure and friction exerted by tools or from frequent accidental blows (manual laborers, such as carpenters, bricklayers, farmers, and shovellers).

A callus consists of a markedly thickened, yellowish to brownish, dense and more or less homogeneous horny layer beneath which a somewhat broadened granular cell layer is found, while the deeper epithelial cell layers are narrowed, compressed and associated with a flattening of the papillae. The cutis exhibits a compression of the collagenous fibrils and an atrophy of the elastic fibrils. The following causative and developmental mechanism is apparently active in the production of these keratotic lesions. While a continuous pressure, such as present in the causation of bed sores, results in a progressive atrophy and ultimately in a necrosis, the intermittent pressure and friction existing with callus formation causes, during the pressure phase, a temporary anemia, and thereby cellular degeneration, which stimulates the keratinizing differentiation of the epidermal cells, whereas the reactive hyperemia prevailing during the pressure free interval permits a compensatory regenerative cellular proliferation (Oppenheim).

Haagensen emphasized that all epitheliomata seen on the hands of carpenters were situated on the dorsal side, while the occupational callosities involved the palmar aspect of the right thumb and of the index finger, whereas the hygromata and soft epithelial thickenings over the bony prominences were found in the palms. In contrast to Mason, who stated that the chronic irritation which leads to the development of calluses of the hands and feet never produces carcinoma, Knox noted that cancers on the basis of calluses of the feet occur very rarely. Baasner stated that 12 out of 190 scar cancers originated in callosities. Considering the enormous number of callosities and of corns on hands and feet, malignant complications arising in them appear to be practically nonexistent.

Several observations suggest, on the other hand, that hyperkeratoses, caused by friction and affecting, usually, areas of the skin where cancers are normally

common and which are exposed to additional exogenous factors of possibly carcinogenic nature (solar rays, tar), ultimately may undergo malignant changes. Haagensen reported the occurrence of an epithelioma of the temple caused apparently by a prolonged friction of the frame of spectacles (1 case). According to observations made by the same investigator, the friction and pressure exerted by the frame of eyeglasses acted in similar fashion in bringing about a cancer of the bridge of the nose in seven cases and cancer of the ear in two cases. Two similar cases of carcinoma of the face caused by ill fitting spectacles were reported by Morton. Stout mentioned the occurrence of a carcinoma of the skin of the lower leg beneath a garter, and Koelsch stated that Mexican mule drivers suffered from scrotal cancer resulting from the friction of the saddle. A bilateral development of a cutaneous carcinoma of the chest at the site where crutches exerted pressure and caused friction was noted by Ullmann.

While such malignant sequelae in the skin as the result of prolonged friction represent exceptional and sporadic phenomena, similar reactions have been seen under corresponding circumstances among domesticated animals. Thus, horses develop hyperkeratoses and calluses in places where there is pressure by the harness. Heller reported the occurrence of cancer of the lower lip in horses at sites of pressure and wounds caused by the bridle. Oxen and buffaloes in India show sometimes a cancer at the base of the right horn where the wooden yoke presses down (Wirth), while such a reaction has not been observed at the left horn which remains free from the yoke (Fibiger).

II. FROST-BITES

Hyde once stated that outdoor life in cold regions does not predispose, apparently, to cutaneous malignancy as skin cancer is rare among the inhabitants of Iceland, Greenland, Faroe Islands and among the Eskimos. There exists, however, a certain amount of more recent clinical and experimental evidence suggesting that frost-bites may serve as a focus of subsequent malignant developments (Fischer-Wasels; Magnussen). Haagensen cited three cases of skin cancer which allegedly developed on the basis of previous frost-bites (a basal cell cancer of the temple was found in a sailor, 78 years old, who said that he had frozen his face several times 38 years previously; a gardener, 68 years of age, developed a basal cell carcinoma of the external ear, which had been frozen 15 years previously and which had shown occasional crusting during the last twelve years; a shipping clerk, 72 years old, had a squamous cell carcinoma of the external ear, which appeared after a frost-bite sustained two years previously and followed by persistent scaling). Von Brunn reported four skin cancers following frost bites among 227 cutaneous malignancies affecting the skin of the extremities. Wainwright mentioned a basal cell carcinoma of the external ear developing in a driver, 62 years old,

following a frost-bite suffered two years previously. A similar case was recorded by Andrews and McNitt, who observed a cancer of the external ear in a coachman who had sustained frost-bites 30 years previously. The ear had remained swollen ever since and a small scab had formed on the edge of the ear. Eckermann noted the occurrence of a squamous cell carcinoma of the foot in a man, 56 years old, whose feet had been frozen and had become partly gangrenous when he was 9 years old. The malignancy started from an ulcer which developed in the stump of one foot following a contusion sustained nine years previously. Treves and Pack as well as Iwamoto observed cancers developing from frost-bites. Pohl mentioned a cancer of the nose in a man, 35 years old, after congelation. Finally a case of sarcoma of the large toe after a frost-bite may be mentioned which appeared in a man, 64 years old, and developed 10 months after the injury in a swollen and ulcerated toe (Leonhard).

Experimental observations reported by Berenblum as well as Mansens support the causal relationship between frost-bites and cutaneous malignancy. These investigators succeeded in producing carcinomas in the skin of mice which had been frozen repeatedly with solid carbon dioxide. It is significant that Berenblum was able to elicit a tumorous response by a single application of carbon dioxide snow, if the skin had been tarred previously. Such neoplastic reactions, however, were obtained only when the necrotizing effect of the carbon dioxide burn was not too severe, as in such a case the superimposition of two "carcinogenic" agents resulted in an inhibition of the carcinogenesis and not in a summation of two carcinogenic stimuli.

Inasmuch as frost-bites are anatomically and functionally equivalent to second degree thermic burns, the development of carcinomas on the basis of frost-bites is comparable to a corresponding phenomenon observed in connection with thermic burns. The causative mechanism operating in bringing about the cancerous response to a nonspecific physical agent is obscure. It may be pointed out, however, that frost-bites are accompanied by the development of rather persistent vascular dilatation in the affected area associated with circulatory disturbances (Leriche and Kunlin). The tumor formation following these injuries occurs most often in regions which are exposed to other carcinogenic, exogenous agents, such as, especially, solar rays. The possible and probable influence of these additional factors is illustrated by the observations of Berenblum in mice which had been tarred in addition to the application of carbon dioxide snow.

III. THERMIC BURNS

Causation. Thermic burns and burn scars appear to be particularly prone to undergo malignant transformations (Arndt). Ullmann stated that 80 per cent of all scar cancers occur in burn scars, while Fischer-Wasels noted that only

scars produced by freezing or burning may form a source of subsequent cancerous developments. The existing evidence indicates that scars resulting from second and third degree burns are especially predisposed in this respect and that the malignancy originates either from a chronic persistent ulcer within the scar, or from a recurrent ulceration, or in a deteriorating scar. Thermic burns which give rise to malignant lesions are caused by open flames, boiling water (scalds), molten metal, hot oil, hot cinders of coal, burning cigarettes, hot pipe stems, or powder explosions, that is by a number of non-specific thermic agents having no chemical or close physical relation to the known exogenous carcinogenic agents, but producing possibly those of tarry nature during their destructive action upon the organic matter composing the tissue. These uncomplicated burn cancers must be distinguished from those in which the burn is produced by a hot specific chemical agent, possessing carcinogenic properties, such as tar, mineral oil, as in such instances the possibility exists that some of the chemical material may be retained in the tissues and may exert a direct carcinogenic effect (Bang; Huguenin; Treves and Pack; Roffo and Gandolfo; and others).

Incidence. The first case of burn scar cancer of the skin was reported by Heurteux in 1860. Additional cases were reported by Broca (1862); Clement (1868); Marcuse (1877); Galard (1892); Jaboulay (1907) and others.

Roffo and Gandolfo observed 22 cases of burn scar cancer; Uchiki as well as Tow and Itoh added five cases each; Johnson as well as Hamont, Bodart and Chalnot recorded four cases each; three cases were seen by Pickerill as well as Haagensen; two cases were reported by Heidingsfeld as well as Eckermann, and one case by Cornil and Lamy; Verdelet; Nuytten and Driessens; Shore; Stauffer; Bang; Arndt; Charbonnel; and MacLeod.

The following data are available concerning the incidence of burn scar cancers among scar cancers in general. Iwamoto found 9 burn scar cancers among 13 cases of scar cancer. Mason recorded 19 burn scar cancers among 98 scar cancers, Baasner noted 33 burn scar malignancies among 190 scar cancers, and Burns recorded 70 burn scar carcinomas among 90 scar cancers. There are thus a total of 391 scar cancers of which 131 originated from burn scars (33 per cent).

The general incidence of burn scar cancers among skin cancers was, according to Meller, 4 among 433 skin cancers; according to Treves and Pack, 30 among 2,465 skin cancers; while the ratio of burn cancers on extremities to cancer in general on these parts of the body was, according to von Brunn, 32 burn scar cancers to 227 cancers in general affecting extremities. Broders stated that 24.59 per cent of all cancers on extremities originate from burn scars, Arndt set this figure at 9 per cent, and DeBell and Stevenson at 10 per cent.

Finally, it may be mentioned that burn scar cancers occur also in animals, as

Drabble reported the presence of the so-called "brand-cancer" in Australian cattle.

Site. The extremities and the head seem to be the most frequent sites of burn scar cancers as these parts of the body are more often exposed to thermic burns than other parts of the body. The following local distribution was noted from an analysis of 88 cases of burn scar cancer: head, 40 cases; lower extremities, 24 cases; upper extremities, 19 cases; trunk, 5 cases. Treves and Pack called attention to the fact that burn scar cancers occur in places where spontaneous carcinomas are very infrequent. They cannot be considered therefore as precocious developments of malignant tumors which would have become manifest normally at some later date.

Vaughan reported, according to White, that burn scar cancer of the hip region occurs frequently in Chinese, as these people sleep on the "Kang," that is a brick structure heated from the inside. Whereas the cancers following burns sustained while resting on this heating appliance are apparently genuine burn scar cancers, those seen among the inhabitants of Kashmir and Japan caused by burns from the use of the "Kangri" or "Kairo," respectively, are classified more appropriately among the soot or tar cancers.

Sex. Burn scar cancers are more frequent among males than females. The ratio of burn scar cancer of males to females was, according to Arndt, 3 to 1, while Treves and Pack reported from a series of 28 cases that 78.5 per cent occurred in males and 21.5 per cent in females. A compilation of 91 cases collected from the literature, on the other hand, gave a ratio of 57 males to 34 females (62.6 per cent and 37.4 per cent, respectively). The sex ratio of skin cancer in general was stated to be 57.5 per cent in males against 42.5 per cent in females (Treves and Pack).

A greater liability of the male to develop burn scar cancer in comparison to the female is apparent from the statistical evidence. This liability, which exceeds the usual preponderance of male over female regarding epitheliomas of the skin in general and which is in contrast to the higher frequency of burns in females than males, is attributed by Treves and Pack to the fact that females, particularly during childhood and old age, die more often from the effects of burns than males because they sustain more often severer burns than males on account of their more easily inflammable attire. Females do not survive sufficiently long the thermic trauma to exhibit its malignant sequelae. The preponderance of males is accentuated by various industrial exposures and other contributory occupational factors (irritation, infection, or injuries) to which males are exposed in general to a higher degree than females, and which act upon the often neglected burn scars.

Race. No reliable information is available regarding the relative cancerigenic susceptibility of burn scars among the members of different

races. DeBell and Stevenson mentioned the presence of a burn scar cancer in a Negro, Treves and Pack saw one in a Negress, and Vaughan made similar observations in Chinese.

Age. The age distribution of 49 cases collected from the literature is presented in the following table.

AGE DISTRIBUTION OF BURN SCAR CARCINOMA

Years	20–30	31–40	41–50	51–60	61–70	71–80	81–90	Total
Cases	4	7	22	6	7	2	1	49

The average age of this series is 48 years, which agrees with the age group in which the peak of the age incidence occurs. Arndt reported an average of 47 years for chronic burn scar cases and of 48 years for acute burn scar cases. Mason gave a slightly higher figure of 51.5 years for burn scar cancers in general, while Treves and Pack noted an average age of 53.5 years for the chronic cases and of 56 years for the acute cases. These discrepancies in the average age of burn scar cancers are probably only apparent ones and are caused by the type of material analyzed. Inasmuch as Treves and Pack pointed out that not the absolute age of the individual, but the age of the scar is the decisive factor determining the development of malignant transformations (Johnson), it is obvious that burns sustained during childhood are apt to result in cancer at a considerably earlier age than thermic injuries suffered during adult life, possibly in the form of occupational accidents. The youngest individual with burn scar cancer, observed by Treves and Pack, was 14 years old and had been burned at the age of 3.5 years. An analysis concerning the average age, based on a series containing an appreciable number of burns sustained during childhood, should yield a lower age figure than that obtained from an evaluation of a series composed mainly of industrial burns.

Latency Period. The length of the latency period varies greatly, ranging from a few weeks to many years. Acute burn scar cancers which develop on the basis of a primary persistent ulcerative defect or within a very young scar have a latency period of a few weeks to several months. Treves and Pack gave an average latency period for acute burn scar cancers of 4 months. Stauffer reported the development of a carcinoma from a burn ulcer in a man, 66 years old, after a 4 weeks interval. A similar observation was made by MacLeod. Cornil and Lamy noted in a man, 26 years old, a malignant development from a thermic ulcerative defect after an elapse of 5 months, while Pickerill recorded the appearance of a cancer within the same period in a man, 45 years old, under similar circumstances. A somewhat longer interval, 2 years, was noted by Pickerill in a second case involving a man 43 years of age. Haagensen listed in one instance an interval of 18 months, the patient being 57 years old. It seems to be characteristic of this group of acute burn scar cancers that the

individuals affected are in general of middle age (average age, 45.6 years) suggesting the presence of preparatory changes in the affected area at the time of the burn. Treves and Pack stated that the average age of individuals with acute burn scar cancers was 52 years at the time of the burn.

Chronic burn scar cancers have a latency period of 32.5 years (average), according to Treves and Pack, and of 23 to 59 years, according to Ullmann. Roffo and Gandolfo gave the following distribution of their cases upon the various decades of latency period: 1-10 years, 8 cases; 11-20 years, 4 cases; 21-30 years, 11 cases; 30-35 years, 3 cases (average, 18 years). In eleven cases collected from the literature the average latency period was 31 years (range, 9 to 51 years: 1-10 years, 1 case; 11-20 years, 3 cases; 21-30 years, 1 case; 31-40 years, 2 cases; 41-50 years, 3 cases; 51-60 years, 1 case). The average age of the individual composing this series was 14 years at the time of the thermic injury, while it was 20 years in the series observed by Treves and Pack (against 45.6 and 52 years, respectively, in two acute series analyzed). The first symptoms of a malignant development (ulceration) in the scar were observed within 6 to 41 years after the accident (average, 22 years), while the primary ulcerative thermic defect never healed completely before cancer ensued after 18 to 51 years (average, 40 years) in three cases.

Causative Mechanism. The causative mechanism active in the production of acute and chronic burn scar cancer is unknown. Some investigators favor the conception that the vascular and nutritive disturbances present in the scar tissue, especially in the large extensive scars often found after burns, play an etiological role, as scar tissue is poorly vascularized and therefore insufficiently nourished, causing it to break down easily and to ulcerate. In burn scars, as in any other scars, there exists an abnormal relation between the epithelium and the connective tissue, which is said to predispose to malignant transformations. Such changes may be stimulated, according to these investigators, by the fact that a scar has no elasticity and reacts therefore more strongly upon a trauma than normal tissue. The presence of folds and nooks in the surface of the scar favor the retention of irritating material, while the configuration of the scar aggravates the normal friction exerted by clothing upon the epidermal lining. All these factors produce, in the opinion of Treves and Pack, a favorable soil for a cancerous change. Whereas these investigators seem to favor the theory of Virchow (chronic irritation as cause of cancerigenesis), Roffo and Gandolfo contended that burn scar carcinomas exemplified the theory of Ribbert, as these neoplasms appeared to originate from misplaced epithelial cell groups. In as much as more or less extensive burns are relatively common, while malignant sequelae arising from them are comparatively rare, it is evident that these concepts of carcinogenesis in burn scars do not offer any plausible explanation.

Treves and Pack proposed, on the other hand, that in the production of acute burn scar cancer tissue, toxins are released by the autolysis and heterolysis of the burn eschar, which may act as direct cancerigenic agents. This conception gains in probability when consideration is given to the fact that during the

thermic destruction of the organic matter substances may be produced which possess carcinogenic qualities, which may be included in the regenerative tissue and thus remain in prolonged contact with the proliferating epidermal cells, and ultimately cause their carcinogenic transformation. Such a conception is supported by the demonstration of necrotic charred matter within the tissue of the burn scar in a few instances (Pickerill; Nuytten and Driessens). Kennaway has demonstrated that human skin subjected to destructive distillation yields a tarry material possessing carcinogenic properties.

There is the possibility that the physico-chemical as well as subsequent proliferative and structural changes of the skin accompanying a burn may activate a precancerous process previously present or that they, in turn, may be stimulated and modified in their course and development by the action of additional exogenous agents, such as solar rays and tarry substances. Thus, Stauffer reported that in his case, senile hyperkeratoses were present at the time of the accident, while in the case recorded by Cornil and Lamy the individual affected was a gardener in North Africa who was exposed to intense solar irradiation. The marked discrepancy between the length of the latency period of burn scar cancers, noted by Roffo and Gandolfo in the Argentine, and that reported by Treves and Pack from the United States, raises the question whether the shorter latency period observed in the Argentine with its sunny climate may be responsible at least in part for the difference present. It may be mentioned that a photochemical action exerted by solar rays seems to have contributed to the development of "brand cancer" in cattle in Australia (Drabble).

Symptomatology—Acute Burn Scar Cancer. These cutaneous malignancies develop in general from relatively superficial and small burns within 1 to 2 years after the accident. A burn of a moderate degree represents rarely the cause of the acute variety of burn of scar cancers (Treves and Pack). The initial injury consists, as a rule, of a blister or an ulcerous sore which exhibits no tendency to heal or which heals only temporarily, to be followed by the development of a small, hard, itching, ill-defined nodule at the site of the former burn. The epidermis covering the elevated papulous growth is either warty or dry, delicate and parchment-like, or there is a button-like, translucent, greyish-red nodule with prominent and dilated capillaries. Ulceration ensues when the precancerous hyperplastic growth is transformed into a malignant one. The cancerous ulcers increase in size and behave in all respects similar to the spontaneous type of cutaneous carcinomas.

Chronic Burn Scar Cancer. Chronic burn scar cancers, which are the by far most frequent type, usually develop from slow forming, extensive and deep burn scars caused by second and third degree burns. The scars may contain ulcers which either have persisted from the time of the original thermic injury or which form later within the scar. The cicatricial tissue may undergo several temporary healings and breakdowns before a malignant transformation ensues. There exists some difference of opinion, whether the thick, dense, deep and sometimes keloid-like type of scar is more liable to cancerous changes (Gold-

blatt) or the more superficial and loose scar (Clement). Ulcers as well as cancers involve most often the central portion of the scar. A burning sensation is felt and darting pains are experienced in the ulcer, when this lesion becomes fixed to its base, while undergoing a malignant change. The ulcer cancers start in general in the crenated and warty edge of the ulcerative defect.

Treves and Pack distinguished between two gross types of burn scar cancer: (*a*) the flat, indurated, infiltrative and ulcerative carcinoma, and (*b*) the exophytic, evertent, vegetative and papillary carcinoma. The ulcerative type is the more common and and may start as a small ulcer attached to the underlying tissue. There may be in the beginning an abortive tendency to spontaneous healing. During the subsequent course, the ulcerative cancer extends infiltratively into the adjacent muscular and bony tissue. The exophytic carcinoma, on the other hand, appears during the early part of its development as a small, indolent and itching papule, which is, at first, firm and later becomes moist and ulcerated, but remains movable for a long time. The course of burn scar cancer is determined to a marked extent by the presence of infectious and inflammatory conditions superimposed upon it, which may stimulate its local and distant spread, and thus may influence greatly its prognosis. Burn cancers show, in the beginning, a rather slow local growth, as the invasive growth of the cancer cells is impeded by the surrounding cicatricial tissue containing obliterated lymphatics. However, after this zone has been penetrated, there occurs a more rapid spread depending upon the proximity of blood vessels, the region involved, the amount and the depth of tissue destroyed. Metastases are formed late and then involve, usually, only the regionary nodes, rarely distant organs. Primary simultaneous or successive multiplicity of cancers in burn scars has been observed repeatedly. Symmetrical carcinomas of both legs developed in one instance following burns of the extremities (Arndt).

Histology. The sloughing of the necrotic tissue in the burned area is followed by the appearance of a granulation tissue, which is gradually transformed into a fibroblastic tissue containing elastic fibrils. In more superficial burns the reepithelization of the defect is accomplished by a proliferation of the epithelial cells of the surrounding intact skin as well as of the glandular elements preserved in the area. In deep burns, however, the appendiceal glands are destroyed completely or small rudimentary epithelial islands are left, so that the reepithelization is interfered with seriously, particularly when the defect is large. In the course of months and years, the connective tissue becomes more and more fibrous and hyalinized, while the epithelization from the margin or from the epithelial islands left in the burned area may or may not have succeeded in covering the defect. In cases in which the healing is delayed or in other ways atypical, ectatic vessels appear within the scar, which then assumes a dark red, hyperemic appearance. The malignant tumors originating on this basis are usually of the squamous cell type, especially when they are derived from deep and extensive burns. But occasionally also basal cell carcinomas are observed, when the burns are more superficial and therefore hair follicles and

sweat glands were spared. Treves and Pack found in a series of 19 cases 16 cornified squamous cell carcinomas, usually of grade I and II, and 3 basal cell cancers; while Roffo and Gandolfo reported in a series of 22 burn scar cancers 2 basal cell carcinomas.

Prognosis. The ultimate prognosis of burn scar cancers is bad in spite of their slow course, because they seem to be resistant to the various therapeutic procedures available (Treves and Pack; Roffo and Gandolfo). The location of the cancer, however, influences to a marked extent the prognosis as it determines the effectiveness of the therapeutic measures which can be taken. Burn scar cancers situated on extremities offer for this reason a better prognosis than those located on the trunk and face because the extremity can be amputated and thereby the malignant growth be removed radically. Other factors influencing the prognosis are extent and local fixation of the tumor, presence of metastases, and inflammatory complications. The prognosis of acute burn scar cancers is said to be more favorable than that of the chronic variety, because acute burn scar cancers are in the beginning more superficial. While Roffo and Gandolfo stated that the majority of burn scar cancers end fatally, Treves and Pack recorded a survival rate of 54 per cent.

Treatment. The therapeutic management of burn wounds must be directed in such a way that it prevents the late development of malignant complications by providing a rapid and good epithelization or epidermization of the defect. The therapeutic measures indicated under such circumstances must obviate the development or eliminate the presence of infectious complications, so that the epithelization is not interfered with. Large and deep defects should be covered at an early date by whole thickness skin grafts. The use of Thiersch's grafts for such purposes is counterindicated as cancers may develop in them (Treves and Pack). If there arises any suspicion as to the benign or malignant nature of a lesion formed in the scar, the scar should be removed radically by surgical measures. Small cancers may be treated with radium or cautery. Local excision or curettage are unsuitable and dangerous procedures.

The use of radium in the treatment of burn scar cancers, however, is a controversial issue. Roussy; Johnson; Strauss; and others contend that radium should not be used, as these cancers appear to be radioresistant because of their high degree of differentiation, the defective vascularization of the scar tissue and its thereby conditioned insufficient regenerative and reparative quality. The frequent presence of infections as well as the early development of radium necrosis in the scar tissue, necessitating the use of relatively low doses, interfere with an adequate and successful radiation treatment of these conditions (Treves and Pack). Roffo recommended, on the other hand, radium for the treatment of small cancers and electro-coagulation for the therapy of large neoplasms. Roentgentherapy proved to be ineffective in the hands of this investigator.

Experimental Burn Scar Cancer. Burckhardt and Müller attempted to produce experimentally burn scar cancer in mice by applying repeatedly over a

period of up to 18 months boiling water or alcohol to the skin of these animals. There developed only loss of hair and atrophy of the skin, but no sign of a neoplastic reaction. These investigators concluded that the negative results obtained militated against the theory that burn scar cancer is the result of a disturbed regenerative proliferation.

Bang produced burns in the skin of several series of mice. Scars were formed at the end of one month. Some of the mice developed a hyperplastic thickening of the skin in the burned area. There was a keratinizing papilloma with early malignant changes in the scar of one mouse 17 months after the treatment, while a second mouse developed an ulcer in the burn scar two months after the treatment, followed two months later by the appearance of a spinous cell carcinoma in the ulcerative defect. In both instances the malignant tumor developed on the basis of a local hyperplastic lesion.

Radiating Heat. Finally, brief mention may be made of the claims which have been advanced connecting a prolonged, occupational exposure to an intense radiating heat with the development of a carcinoma of the skin on the basis of chronic thermic tissue changes. Murray stated that shin cancer is supposed to be the penalty of stokers, who are exposed to intense direct thermic irradiation. It is maintained by this investigator that carcinoma of the lower leg is found frequently in England among locomotive firemen and engineers caused by the intense heat from the firebox striking the shanks (Haagensen). Haagensen, on the other hand, did not find any similar case among the numerous engineers who were observed at the Memorial Hospital because of neoplastic disorders. Commenting on this fact, Haagensen mentioned, that F. C. Wood had pointed out that the American railroad engines were constructed differently from the English ones, in that the legs were not exposed to excessive heat when firemen attended the fire. However, Ullmann contended that the anterior aspect of the lower legs of stokers was not only a site of cancer, but that also the extensor side of the right forearm of locksmiths exhibited the same predisposition because of an undue occupational exposure to excessive radiating heat.

Apart from the fact that the occurrence of cancer of the leg in English engineers is a rather vaguely documented observation, White called attention to the fact that radiating heat is more and more ruled out as a carcinogenic agent. However, even if the actual existence of carcinomas of this location among the members of this occupational group is conceded for the matter of argument, it appears to be more likely that the unavoidable and simultaneous exposure to soot associated with the attendance of boilers and furnaces and not the radiating heat represents the actual carcinogenic agent, while the thermic hyperemia assumes merely the role of a contributory factor.

IV. SCARS

In 1828 Marjolin published his classical description of carcinomatous ulcers developing in scars. Scar cancers are known since that time as "Marjolin's

ulcers". Additional cases of scar cancer were recorded by Hawkins in 1835, who mentioned particularly the occurrence of epitheliomas in old scars on the backs of soldiers who had been forced to run the gauntlet. The number of scar cancers was increased further by the reports of Pherson and Howsat (1844); von Volkmann; Chaintre (41 cases); von Brunn (7 cases); Röpke; Coenen; Melchior; Meller (5 cases); Mohr; Theilhaber and Theilhaber; Lawson; Jarowitzky; Martinelli; Boegehold; Just; Katayama; Treves and Pack; Goebel; Iwamoto; Uchiki; Nimet; Lumière; Schad; Montpellier, Goinard, and Fabiani; Watrin and Sorlat; Mouchet; Delannoy and Driessens; Burns; Maiditsch; Lavau; Bang; and many others.

The nature of the injury varies greatly with the individual cases (laceration, wounds associated with compound fractures, gun shot wounds, avulsion of scalp, etc.). The scars are in general slow in forming as the healing of the wound is often delayed by purulent processes. A second injury involving the scar is associated in several cases with the onset of the malignant development. The latency period is said to be the longer, the earlier in life the primary cutaneous lesion is produced. The latency period is very prolonged in the great majority of cases, being usually from 20 to 40 years, rarely less (Katayama; von Brunn). There exist, on the other hand, several cases in which the malignant development followed after a shorter interval after the accident (6 months to 3 years) (Lavau; Mouchet; Montpellier, Goinard and Fabiani; Schad; Maiditsch). Traumatic scar cancers appear often at an earlier age period than skin cancers in general. This phenomenon is attributed to the fact that not the age of the individual, but the age of the scar is the more important factor in determining the time of malignant transformation (Ullmann). Men are involved more often than women. The extremities, especially the lower ones, are the most frequent site of scar cancer.

Lumière considered the following four conditions as essential for the cancerization of a scar: (*1*) slow formation of the scar; (*2*) prolonged malnutrition or aging of the scar (20 to 50 years); (*3*) secondary trauma to the scar; (*4*) adequate humoral environment. Inasmuch as the first three mentioned pre-conditions are present in a great number of scars which never become malignant, their actual significance for the process of cancerization is evidently doubtful. The fourth factor noted is more or less of assumptive and speculative nature. In view of the great rarity with which cancer formation ensues in scars, it appears probable that such extraordinary developments are caused by the presence and action of one or several additional factors, possessing specific properties, in or on the scar tissue. Such influences may be found possibly in certain exogenous agents of environmental, occupational or medicinal nature.

There exist, according to von Brunn, two different types of scar cancer: (*1*) a nodular, papillary, fungoid, broad based or plaque-like tumor; (*2*) an ulcerated lesion with elevated, irregular edges and a nodular floor. The great majority of these neoplasms are cornified squamous cell carcinomas and only a

few are of the basal cell variety. As the cancer originates usually in the central portion of the scar, it is surrounded by cicatricial tissue and has therefore the tendency to spread in the beginning more on the surface than into the depth, where its progress is impeded by the fibrous tissue (Iwamoto). Because of this type of proliferation of scar cancers, their late metastatization into the regionary lymph nodes, and their frequent location on extremities permitting their radical removal by amputation, the prognosis of this type of traumatic carcinoma is more favorable than that of skin cancers in general (Iwamoto; Treves and Pack).

Concerning the medico-legal and social aspects of scar cancer, Wainwright pointed out that the late occurrence of these tumors in scars of industrial injuries should cause the removal of time limitations from the compensation laws.

V. VARICOSE ULCERS

Varicose veins and their ulcerative sequelae of the lower limbs are relatively common conditions, which are particularly frequent in those individuals who are forced to stand more or less on one spot during their occupational activities (laundresses, shop girls, or waitresses). The skin above and adjoining the varicose, subcutaneous veins becomes ultimately thinned, atrophic, edematous, increasingly pigmented and eczematous, while dilated tortuous capillaries, sometimes forming spiderweb-like patterns, are found near the larger veins, giving the involved area, because of the existing passive congestion, a pinkish red to dark purple color (Biegeleisen). Ulceration in the altered skin occurs either spontaneously or as the result of some mechanical injury. These ulcerative defects are shallow in the beginning, but later may become deep and crater-like, and may develop thick, elevated, callous edges. Because of their torpid character, the ulcers often exhibit very little tendency to heal, and, especially, if the causative, unfavorable static, occupational conditions continue. These ulcers may persist for many years and may reach large proportions, sometimes encircling the leg.

While the chronic inflammatory conditions as well as the presence of prolonged circulatory disturbances resulting in nutritional disturbances of the affected tissue should represent a favorable soil for the development of malignancy, according to the conceptions incorporated in some theories of carcinogenesis (Virchow; Warburg), it is a well established fact that cancerous complications of varicose leg ulcers are rare (White; Mason; Gottheil). Their behaviour in this respect does not differ from that of the corresponding varicose conditions of the recto-anal region, the hemorrhoids.

Gottheil expressed the opinion that the chronic dermatitis, accompanying varicose ulcers, and not the vascular and circulatory disturbances, represents the cause of a malignant transformation in a varicose ulcer. It has been observed that the malignant change sometimes occurs simultaneously with, or soon following, the onset of an acute eczema in the chronic varicose and ulcerated skin.

De Jong, Meyer and Martineau noted, on the other hand, that malignant development not infrequently ensues after the application of a tar preparation to a varicose ulcer. This sequence of events deserves special and serious consideration, as it is still common practice to use epithelial proliferation stimulating ointments, containing scarlet red and related substances, in the treatment of these sluggishly healing ulcerative defects.

While the cause or causes for an exceptional malignant transformation of crural varicose ulcers are unknown, it seems to be possible that they are not so much related to endogenous factors as to specific exogenous ones.

The following data are available concerning the incidence of cancerous transformations in varicose ulcers of the leg. Nobb found one such tumor among 200 cases of crural varicose ulcers present in 4,000 inmates of an old age institution. De Asis observed one malignant complication among 310 cases of varicose ulcers of 6 months to 30 years' duration, present in individuals of cancer age. Tenopyr and Silverman analyzed 1,000 cases of chronic ulcer of the leg and noted 4 cancers which developed on the basis of these crural lesions. Grosser reported that only 6 carcinomas among 368 carcinomas of the extremities developed on the basis of a varicose ulcer. Michael, on the other hand, recorded 8 cases of malignant varicose ulcer among 26 cancers on the extremities. Additional individual cases were reported by Knox (2 cases); von Volkmann (24 cases); Druckenmüller (2 cases); Mondor and Olivier; and others. A bilateral occurrence of carcinoma in varicose ulcers was reported by Druckenmüller as well as Grosser.

While varicose ulcers are more common in men than in women, Knox noted a practically equal distribution of cancers of this genesis among the two sexes (53 cases: 28 males, 25 females). The age distribution of 49 cases was as follows: 30-39 years, 3 cases; 40-49 years, 13 cases; 50-59 years, 14 cases; 60-69 years, 17 cases; 70-79 years, 2 cases. The duration of the ulcer preceding the onset of the malignant development varied, in 28 cases, between 10 and 40 years (average, 21 years) and was seldom shorter (6 months) (White).

The onset of malignancy was often indicated by the appearance of increased pain and the rapid growth of cauliflower-like masses in the margins of the ulcer as well as by a rapid extension of the crater. The ensuing neoplasm was either of the fungoid or of the infiltrative type. Because of the existing impaired blood supply, a relatively slow growth rate was observed, while metastases occurred late on account of obliterated lymphatics existing in the dermatitic skin. The carcinomas were of the epidermoid variety.

Attention may be called to the fact that carcinomas of the lower limb, originating on the basis of a chronic ulcer, are more frequent among the inhabitants of the Dutch East Indies, where crural infectious ulcers are more common than among the population of northern climates (Bonne).

VI. OSTEOMYELITIC FISTULAS

Epidermal malignancy may arise occasionally in and around chronic osteo-

myelitic fistulas, developing either upon a hematogenous infection of the bone or upon accidental compound fractures or gun shot wounds (von Brunn; Scheid; Harrison; König; Hobart and Miller; Hellner; Eliason and McLaughlin; Henderson and Swart; Benedict; Devars; Collins; Blanco; Wakeley; Hawkins; Zumhausen; Brunschwig; Placinteanu and Dobrescu; Pohl; and others). Hellner found in the German literature (1838-1934) only 41 such cases. The following data on the incidence of such a complication are available. Hobart and Miller found 3 cases of fistula carcinoma among 108 cases of chronic osteomyelitis (2.6 per cent). Benedict reported 12 cases of epidermoid carcinoma of the fistulous tract in 2,400 cases of osteomyelitis (0.84 per cent). Henderson, on the other hand, found only five cases of this type among 2,396 cases of osteomyelitis (0.208 per cent). A similar incidence figure was given by Harrison (0.27 per cent), who saw only one case with a cancerous complication during 22 years among 365 cases of osteomyelitis.

Osteomyelitic fistulas involving the tibia seem to be most prone to develop malignant complications. In a series of 39 cases of osteomyelitic fistula carcinoma, collected by Harrison, 26 affected the tibia, 5 the femur, 5 the bones of the foot, 2 the bones of the arm, and 1 the knee. Eliason and McLaughlin observed a bilateral carcinoma of the fistulous tracts of both tibias in a man, 34 years old, who had sustained a compound fracture at the age of 6 years. The latency period of this condition varies from 20 to 50 years, but sometimes a shorter period is observed [1 to 3 years (Hobart and Miller; Collins; Devars)]. Hellner found a latency period of more than 40 years in 14 cases, and of less than 20 years in 6 cases. The average age of the individual with fistulous cancer is approximately 50 years, rarely less (Harrison: one case, 13 years old; Hellner: one case, 25 years old).

The onset of a malignant development in an osteomyelitic fistula is indicated by the appearance of severe pain, and of an increased amount of foul, purulent discharge. The diagnosis of the fistulous cancer is relatively easy as long as the tumor involves the visible parts of the sinus, but becomes difficult if the malignant focus is deep-seated. Biopsy and sometimes radiographic examinations must be used then for the establishment of the diagnosis (Benedict). The histological examination of such lesions reveals a diffuse and extensive invasion of the adjacent soft and bony tissues by epithelial cells containing numerous mitoses. Distant metastases, however, are rare (Hellner), as the malignant growth displays a tendency to remain localized for a long time. The prognosis of osteomyelitic fistulous carcinoma is therefore favorable, particularly because of the possibility of its radical removal by amputation of the affected limb.

Chronic irritation cannot be considered as an adequate cause of the osteomyelitic fistulous carcinomas because of the rarity of such a complication in osteomyelitis. Similar objections must be advanced against the conception of a derailment of the regenerative process as the causative factor. It is entirely speculative whether or not aromatic protein degradation products, such as

indol or skatol, under certain circumstances may act as specific etiological agents (Scheid).

In addition to the epidermoid carcinomas originating from the heterotopic epithelium of osteomyelitic sinuses, there occurs a second type of epitheliomorphic neoplasm in the tibia, which exhibits a marked relation to trauma. These tumors reveal a structure identical with the adamantinomas of the jaw. There are fourteen such cases on record, in the majority of which a trauma to the shin preceded the onset of the tumor growth (Fischer-Wasels; Ryrie; Holden and Gray; Rankin; Dunne; Baker and Hawksley; Bishop; Casini; Rehbock and Barber; Richter; Thomas; Wolfort and Sloane; Davidson). The latency period varies from one month to 8 years. The age range is from 22 to 46 years. Males are involved in most cases. The tumors grow slowly and do not form metastases. Two theories exist concerning the genesis of these neoplasms: 1) Fischer-Wasels maintains that they originate from epidermal cells of multipotential type, misplaced into the bone during an early part of the embryonal period when the tooth germ was formed, and which were activated into a neoplastic proliferation of a highly specialized type by the traumatic stimulus; 2) other investigators (Ryrie), on the other hand, contend that small groups of epithelial cells can be readily displaced into the periosteum by a grazing injury to the skin closely covering the shin-bone.

In view of their distinct medico-legal significance, it is important that these adamantinomas of the tibia are not confused with tumors of endothelial origin which sometimes have an epitheliomorphic appearance (Bursell and Gellerstedt).

VII. MELANOMAS

Melanotic nevi, which are congenital malformations that appear usually at an early age, and in multiple number, in the skin of the great majority of white skinned people, and which are also not rare in the skin of colored races (Hewer), give rise exceedingly rarely to malignant growths (melanocarcinoma, melanosarcoma, malignant melanoma, melanoblastoma, nevocarcinoma), reflecting in their terminology variations in the morphology of these tumors, and also the controversial character of their histogenesis (epidermal, mesodermal, neurogenic).

A large number of allegedly traumatic nevocarcinomas have been recorded (Schopper; Jones; Hertzler; Heller; Treves and Pack; Specht; Quensel; Bashford; Gougerot and Burnier; Dawson and Wehr; Hewer; Matras; and others). A causal relationship between a trauma to a nevus and the subsequent development of a malignant melanoma from this lesion existed in 4 out of 22 cases of melanocarcinoma, according to Gleave; in 10 out of 50 cases, according to Butterworth and Klauder; in 11 out of 27 cases, according to Amadon; in 32 out of 159 cases, according to Farrell; in 17 out of 36 cases, according to Coley and Hoguet; in all of 15 cases of melanocarcinoma of the foot, according to Stevenson; and in 6 out of 7 cases, according to Hazen. Résumé: in 95 out of 306 cases of nevocarcinoma, or approximately 30 per cent.

The traumatic influences incriminated in the malignant activation of a nevus were in general of chronic nature, such as prolonged friction or continuous pressure, exerted especially upon protruding nevi. Other injuries mentioned were bruising, cutting, burning injuries, improper therapeutic procedures, such as incomplete surgical removal or strangling of pedunculated nevi with a thread. In some of the cases a penetrating wound, caused by nails, tacks, or thorns, was blamed for producing not only a traumatic misplacement of pigmented elements into the subepidermal layer, but also for providing the malignant stimulus to this "implantation melanoma" (Eve; Farrell; and others). Additional circumstantial evidence, indicating that a single or repeated trauma may occasionally elicit the development of a melanocarcinomatous response in the skin in the absence of a preexisting mole (Dawson; Ewing), is supplied by the fact that only a part of the malignant melanomas originates from pigmented nevi (Broders and McCarty, 50 per cent; Horowitz, 36.7 per cent; Farrell, 60 per cent).

The apparent etiological significance of trauma in bringing about a cancerous transformation of a quiescent pigmented nevus is indicated by the type of local distribution of these neoplasms and its relation to certain racial aspects. Malignant melanomas, derived from moles, occur most often in areas where these congenital malformations are exposed to frequent trauma and irritation (scalp by combing; cheeks by shaving and scratching; lips by biting or smoking; neck, clavicle, waist, axillary, inguinal and genital regions, ankles and feet by friction of clothing or by penetrating injuries (Nicholson), if the individuals go barefooted). The areas of predilection are the head and the lower extremities, especially the feet (Farrell; Matras). In a series of 50 cases, reported by Butterworth and Klauder, 11 were situated in the face and neck, 18 on the lower extremities, 6 on the upper extremities, 13 on the trunk, 8 on the shoulders and back, 1 on the penis and 1 on the perineum. In a series of 598 cases of melanocarcinoma collected from the literature and analyzed by the same investigators, 16.5 per cent involved the head, 7.7 per cent the neck, 15.5 per cent the trunk, 2.7 per cent the genital and anal regions, and 52.3 per cent the feet. Schreiner and Wehr observed in a series of 10,459 malignant tumors, 37 neoplasms involving the feet of which 17 were melanomas.

It is important in this connection to observe that melanomas occur more frequently on the feet of African Negroes who go barefooted and are exposed to injuries by thorns and infections than on the feet of American Negroes, who more generally wear shoes and are thus more effectively protected against trauma to the soles (Hewer). Similar observations among members of various colored races were made by Gilchrist; Wieting and Hamdi; Bashford; Sutton and Mallia; Dawson; Dickson and Jarman; and Stevenson. Mention may be made that melanocarcinomas in colored races not only affect the soles, that is, one of the least pigmented parts of their skin, but also, although less often, affect other portions of their body surface (Butterworth and Klauder;

Hewer; Stevenson; Bauer; Bishop; and others).

Whereas it is emphasized usually that melanomas are rare in colored races (Butterworth and Klauder; Anderson; Pack and Adair), such information is not reliable. It may be possible that differently pigmented human races show similarly varying liabilities toward the development of melanomas as those displayed by horses, among which white horses are most susceptible to these neoplasms.

Traumatic factors are incriminated in the causation of the relatively uncommon subungual melanocarcinomas which may arise in the nailbed or nailfold either on the basis of a preexisting subungual nevus (Heller; Wurmbrand; Rochoch), or without such preformed anlage (Watson; Womack). Traumatic subungual melanomas among members of the white races were described by Specht and Quensel; Jones; Wurmbrand; Hertzler; Heller; Schopper; and others. While Pack and Adair (1 case in Negro); Bonne (2 cases in Negroes); Dickson and Jarman (1 case in Negro) and Hewer (2 cases in Negroes) observed such neoplasms among colored races. It is of interest that the nailbed, just as the sole, belongs to the normally least pigmented parts of the body in colored races. The absolute incidence of subungual melanomas is not high (Farrell: 6 subungual melanomas among 265 melanomas; Affleck: 6 subungual melanomas among 266 melanotic tumors; Pack and Adair: 20 subungual melanotic neoplasms among 695 melanocarcinomas or 3.4 per cent). Local distribution of these tumors is reflected by the statistical data provided by Pack and Adair: Of 477 melanomas, 74 or 15.5 per cent were situated on the foot and 6 of these were of the subungual type (8.1 per cent); 29 melanomas affected the hand (6.1 per cent), of which 34.5 per cent were of the subungual type. The great toe and the thumb seem to be most often the site of these blastomas.

Whereas melanomas were observed occasionally in the very young as well as in the very old, the majority of cases affected individuals of middle age. The average age reported by Butterworth and Klauder was 49 years, and the average age of their collected series of 146 cases was 47 years. A similar age figure was obtained by Pack and Adair for their series (47.9 years for melanomas in general; 58.7 years for subungual melanomas).

The causative mechanism active in the transformation of quiescent pigmented nevi into malignant melanomas is not known, but probably it is not different from that operative in any other type of tissue. Nevus cells in general are a priori neither precancerous nor malignant (Bloch; Guggenheim), nor do they appear to be appreciably more predisposed to undergo malignant transformation than other normal cells (Butterworth and Klauder). Ewing emphasized that the great majority of nevi are entirely harmless. In as much as the great majority of malignant melanomas occur during middle and advanced adult age, nevus cells do not seem to possess inherited malignant potentialities, because such qualities usually result in tumor formation at an early age. It seems to be likely that trauma merely activates a preexisting and, pos-

sibly, an acquired cancerous tendency in nevi, or creates the environmental conditions suitable for the action of more specific cancerigenic factors.

It has been said that bluish black to slate black, flat or slightly elevated pigmented moles possess the most marked disposition toward a malignant transformation (Eller). The onset of such a development is indicated often by an increase in the size and in the intensity of pigmentation of the nevus. This is followed later by crusting and bleeding from the growing lesion. While radical surgical removal of suspected or early malignant nevi offers the only chance of cure, the ultimate prognosis of malignant melanomas is very unfavorable, because these tumors metastasize very early, both by way of the lymphatics and of the blood stream into remote organs, which are sometimes studded with secondary deposits. These appear often in showers.

It may be pointed out in this connection that the histological differential diagnosis between a benign nevus and a beginning malignant melanoma is not infrequently very difficult and sometimes cannot be made with absolute reliability. The histological diagnosis of malignant nevi has to be based upon the demonstration of atypically arranged nevus cells, atypical cellular and nuclear structures, reactive changes in the surrounding vasculo-connective tissue and invasion of nevus cells into lymphatics and blood vessels. It is advisable to take into consideration in doubtful cases the pertinent clinical and historical data before a definite diagnosis is made on the basis of histological evidence. This procedure is indicated by the fact that sometimes the biological malignancy of nevi seems to precede the histological one (Schürch).

VIII. MEDICO-LEGAL ASPECTS OF TRAUMATIC EPITHELIOMAS

Medico-legally, acute traumatic cutaneous malignancy presents obviously greater difficulties in the establishment of causative interrelations and therefore requires closer scrutiny of the circumstances surrounding the development of the allegedly traumatic tumor, than is the case regarding cutaneous neoplasms attributed to the effects of chronic irritation or repeated injuries of an accidental or occupational nature. These agents have been accepted as provocative causes of precancerous lesions, as the evidence for such damages (Pack; Ewing; Moran) in court, especially in industrial workers, has been sufficiently conclusive to secure monetary compensations.

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III

OCCUPATIONAL TUMORS OF THE ALIMENTARY SYSTEM

1. ANATOMICAL AND ETIOLOGICAL CONSIDERATIONS

THE alimentary tract, consisting of lips, oral cavity, tongue, pharynx, esophagus, stomach, intestine and the two large digestive glands, the liver and pancreas, represents one of the three chief ports of entrance of exogenous agents. It is, also, an important organ system for the metabolic conversion and excretion of exogenous agents, which have entered the body through the skin, respiratory organs, and alimentary system. In spite of the intimate and intense contact of numerous occupational and non-occupational, extraneous agents, some exhibiting well-established noxious or cancerigenic properties, with the tissues of the digestive system, no generally recognized occupational tumors of the alimentary organs exist. Statistical evidence, scattered and isolated clinical observations as well as experimental findings, indicate strongly that a causal relationship possibly exists between occupational hazards and the occurrence of neoplasms of the digestive organs, and that there are good reasons supporting the probability of such interrelations. A thorough analysis, detailed presentation, and discussion of the evidence available seems to be in order, as cancer of the gastro-intestinal tract accounts for 50 to 65 per cent of the total cancer mortality of white males.

2. STATISTICAL INVESTIGATIONS IN DIFFERENT OCCUPATIONAL GROUPS

In a statistical investigation, based on the analysis of 46,118 cards of the Registrar General in England and Wales, Young and Russell found an excessive mortality from cancers of the alimentary organs in the following occupations:

1. Cancer of the tongue: Men employed in liquor trades, or liquor consumers for occupational reasons (brewers, messengers, porters, dock workers, butchers, and costermongers); and to a lesser extent, tobacconists, slaters, tilers, cutlers, printers, and plumbers.

2. Cancer of the esophagus: Men employed in the liquor trade and liquor consumers (brewers, innkeepers, beer bottlers, travelling salesmen, coachmen, cabmen, wharf laborers, and costermongers), and metal workers (plumbers, brass and bronze workers, tool workers, and electric apparatus makers).

3. Cancer of the stomach: Workers engaged in mining and quarrying (iron

mines, lead mines, slate quarries, and coal mines), and manufacturers of wool and cotton goods.

4. Cancer of the intestine: Men engaged in sedentary work conducive to constipation and auto-intoxication (barristers, solicitors, clerks, civil service officers, and clergymen).

From an analysis of these data, Young and Russell concluded that there is a definite tendency toward a direct association between mortality from lingual cancer and that from esophageal cancer, while no significant relationship exists statistically between lingual cancer and gastric, intestinal, and rectal cancers. The same absence of a significant statistical correlation was noted regarding gastric and rectal cancers.

Reports of the International Labour Office indicated that slaters, brush-makers, wiredrawers, cutlers, tobacconists, hair dressers, brewers, messengers, and iron founders have an excessive liability to cancer of the tongue. Behla and Koble claimed that esophageal cancer is prevalent among furriers, photographers, brewers, electric apparatus makers, and scientific instrument makers; gastric cancer showing excessive incidence among miners (iron and lead), slate quarriers, wool sorters, cotton weavers, electricity supply workers, and makers of bicycles. In a report of the Registrar General in England, in 1928, it was suggested that individuals exposed to tar products exhibit a marked susceptibility to cancer of the skin and of other sites, including the lips, tongue, mouth, jaw, and stomach. It mentioned that the incidence of cancers of the tongue, esophagus, and stomach increased from the highest social group toward the lowest social group (V) (unskilled workers).

A similar conclusion was reached by Cramer from an analysis of the mortality statistics of Wales and England. This author pointed out that the incidence of gastric cancer is not dependent so much upon some especially dangerous occupational exposure, as it is related to the social scale, since gastric cancers become more frequent as one descends the social scale. In support of this Cramer cited statistical data, supplied by Hang, obtained from a study of the gastric cancer mortality among various occupational groups, and representing a sliding scale of social classes in Bavaria from 1924 to 1928.

Social Class Occupation	Percentage of Gastric Cancer in Total Cancer Mortality
I. Merchants, doctors, and high officials	38.8
II. Office workers	40.1
III. Publicans, brewers, and small officials	48.5
IV. Skilled workmen	56.8
V. Unskilled workmen	63.4
VI. Agricultural laborers	68.5

Peller called attention to the fact that occupations with tar contacts exhibit an elevated incidence of skin cancer and cancer of certain internal organs (stomach, intestine, alimentary glands, and urinary organs), showing, at the same time, a lowered frequency of cancer of the lip, tongue, and esophagus. The following compilation was offered in support of this claim.

Site of Cancer	Social Class V o/oooo	Special Members of Class V Having Contact with Tar, with Consideration of Same Age Grouping*
Skin	8.6	62.8
Lips, tongue, and esophagus	37.7	22.6
Stomach	50.3	57.1
Other organs	122.0	159.2
	218	302

* Spinners, gas stokers, and chimney sweeps.

Peller mentioned that similar differences in the incidence of cancers of the digestive tract exist in social class IV in regard to its members employed in alcoholic trades. The statement of Peller, concerning the excessive incidence of cancers of the digestive organs in individuals exposed to tarry substances, is somewhat confirmed by an observation of Kennaway in connection with malignancies in chimney sweeps. Kennaway noted that among 65 cancers found in chimney sweeps, from 1910 to 1912 in England and Wales, 18 affected the scrotum and penis, while 83 per cent of the non-scrotal cancers were located in the alimentary system. An unusually high incidence of gastro-intestinal malignancies was found by Teleky among chromate workers (5 gastro-intestinal cancers among 44 deaths). A similar claim was advanced by Turner and Cole in regard to workers employed in smelting plants.

These incomplete statistical data may suffice to illustrate the uncertain and contradictory character of the evidence obtained in regard to the occupational incidence of alimentary malignancy. General agreement seems to exist upon one point; namely, an excessive frequency of cancer of the digestive organs is present in individuals exposed for occupational reasons to tar or tarry products.

3. TUMORS IN THE VARIOUS ORGANS OF THE ALIMENTARY SYSTEM

a. Lips

Carcinoma of the lip is characterized by three outstanding features: 1. It is more common in men than in women (ratio 10 : 1) (Fricke; Lane-Claypon; Eggers; Wile and Hand; Elliot; Kelly; and Hyndman); 2. The predominant

site is the lower lip [93 to 95 per cent; only 5 per cent being located on the upper lip and 2 per cent at the angles in men; but 25 per cent are found on the upper lip in women (Wile and Hand; and Delarue and Fayein)]; 3. The most frequent histological type is the squamous-cell carcinoma with or without cornifications. The basal-cell carcinoma is rare and usually found on the upper lip, involving the skin; in contrast to the carcinoma of the lower lip, which originates from the mucous membrane. These relationships undergo certain alterations whenever some exogenous cancerigenic agents of occupational or non-occupational (habit) origin exert a special influence upon the development of cancers of the lip.

I. CHEMICAL AGENTS

Cancer of the lip, based on an occupational exposure to carcinogenic agents (tar, pitch, and crude oils), is observed in members of various occupations (gas plant workers, stokers, tar workers, roofers, fishermen, and spinners) (Barthe; Irvine; Teutschlaender; Haagensen; Legge; Manouvriez; Kennaway; Heller; and Shambaugh). In his classical description of pitch cancer among pitch and tar workers, Manouvriez mentioned the occurrence of a cancer of the lower lip in a charger among a total of nine cases of pitch cancer recorded. In an extensive survey of occupational cancer in England and Wales for the years 1920-1923, Kennaway listed, among 100 cases of pitch cancer, thirteen located on the lips. Among 19 cases of tar cancer, which had been observed in New York hospitals from 1920 to 1927, there was one case of lip cancer in a stoker employed in a gas works (Heller). The same author found a second case in a mixer employed in a factory in Cleveland, Ohio, where carbon black was produced from calcined carbon flower mixed with light tar oil and tar. Three additional cases of lip cancer, caused by occupational exposure to tar, were seen by Heller in the same plant among workers exposed to coke-oven pitch. They were considered by him as non-occupational in nature, as coke-oven pitch was less irritative than gas tar. These four cases of lip cancer represented 20 per cent of the total number of skin cancers observed in this plant (21 cases).

There were six cancers of the skin in a French gas and pitch plant, employing between 1,100 and 1,400 workers per year from 1921 to 1936. Two were located on the lips (one basal-cell cancer on the upper lip and one squamous-cell carcinoma on the lower lip), in addition to 23 cancers of the internal organs and one myeloid leukemia (Barthe). The occurrence of precancerous pitch warts on the lips of pitch workers was recorded by Teutschlaender in 17 out of 112 cases with pitch warts, and by Legge in 7 out of 53 cases. Two cases of carcinoma of the lip in roofers (one of them located on the upper lip) and two cases on the lower lip in gas workers, among a total of 20 occupational cancers of the skin caused by contact with tar, were mentioned by Haagensen, who emphasized the etiological importance of tar for the production of the epithelial malignancy of this organ.

The significance of this statement is illustrated by the report of Shambaugh concerning the frequent occurrence of lip cancer among fishermen exposed to tar. These men are prone to develop this malignancy, as tar is used extensively in the fishing industry to impregnate nets. The men having the most intimate contact with tar are those employed in the "net lofts," where nets are repaired and tarred. While mending the nets these men have the habit of holding the tar-smeared wooden needle between the lips on the right side of the mouth. Thus a frequent and close contact of the lips with the carcinogenic agent is established. As their hands and fingers are smeared also with tar, there exist additional opportunities of an exposure of the lips to tar, when these men eat their meals or handle their pipes. While these fishermen are out at sea, the tar smudge may stay on the lips for weeks. Lip cancer among net repairmen is not rare, but it has not received the proper attention, as the lip cancer in fishermen has been attributed usually to other causes.

In a series of 79 cases of lip cancer, observed between 1932 and 1933 in the Huntington Memorial Hospital at Boston, five cases were contributed by fishermen (Shambaugh), two of whom used to place the wooden needle between their lips. The same investigator collected from other sources an additional three cases of lip cancer in fishermen (total of 8 cases; 4 held needles between lips; 3 repaired nets; 1 used tarred nets) and had seen two cases previously. The lower lip was affected in all cases. The cancers were of the epidermoid type. The age range of this group was from 41 to 73 years (3 cases were 40 to 49 years old; 2 cases were 50-59 years of age; 4 cases were from 60 to 69 years old; and 5 cases were in their eighth decade). The time of exposure to tar varied from 5 to 60 years (5, 6, 10, 30, 40, 56, and 60 years, respectively).

The tar etiology of these lip cancers was supported by the fact that the loft workers, who remained indoors and were not exposed unduly to sunlight, suffered not infrequently from tar cancer of the face (cheek), which was occasionally multiple. The possible causal significance of pipe-smoking in the production of these cancers could be disregarded, as two of ten cases observed by Shambaugh did not use tobacco at all, and six of the remaining 8 men held their pipes on the side of the mouth opposite the cancer. Similar observations regarding the occurrence of tar cancer of the lip in fishermen were reported recently by Beck, who noted the excessive incidence of this type of malignancy among the fishermen in Campbeltown, Scotland. In mending their nets these fishermen put the bone or wooden needle, threaded with tarred twine, between their lips and established frequent and prolonged contact with this carcinogenic agent. When the tar-creosote mixture used by the fishermen was tested for the presence of carcinogenic properties by applying it to the skin of mice, papillomas were obtained within 106 days, and carcinomas of the cornifying squamous-cell type appeared later. The causal relationship between the par-

ticular occupational activity and the occurrence of lip cancers among fishermen of this vicinity was proven satisfactorily.

Some evidence, as yet uncertain, exists, suggesting that the occupational contact with crude oil may be related to the causation of cancer of the lip. A rigger, employed in a petroleum refinery, and a machinist were listed by Haagensen with cancer of the lower lip. This investigator maintained that in these cases the occupational factor was irrelevant. This conception is supported by the statistical data supplied by Irvine in regard to the occurrence of lip cancer among cotton mule spinners and related workers employed in the textile industry. Whereas 133 skin cancers were noted in 1,502 mule spinners, there was not a single tumor located on the lips. This observation of Irvine would indicate that the occupational contact of the skin with a crude oil, having well-established carcinogenic properties, may cause cutaneous cancers in many parts of the skin with the exception of the lips. Heller lists among a larger series of skin cancers, resulting from occupational exposure to crude oil, a cancer of the lip in an oil pumpman.

No reliable information is available as to whether or not contact of the lips with coal-tar dyes may initiate or contribute to the development of labial malignancy. Haagensen mentioned one case of lip cancer in a packer of dyed cloth, which was regarded by him as of non-occupational nature.

II. HABITUAL ASPECTS

In the etiological, differential diagnosis of occupational cancer of the lip, serious consideration must be given to the causative role which the smoking habit plays in the production of these neoplasms. The evidence supporting this conception is chiefly of circumstantial, clinico-statistical nature. Pipe-smoking is the most seriously and frequently incriminated type of smoking. It is argued that porous clay pipes, and pipes with wooden stems permit the seepage of the tarry distillation products, and bring about their direct contact with the lips. In a number of cases the cancer definitely appeared on the site of the smoker's patch or leukoplakia, where the pipe had rested for years (Wile and Hand; Eggers; and Broders). This mechanism would account for the location of the cancer on the lower lip, as the pipe juices would tend to penetrate through the dependent side of the pipe stem. In addition to the chemical factor, a physical factor, the heat of the pipe stem, especially if the stem is made of metal, may contribute to the causation of the neoplastic growth. Heat will increase the permeability of the mucosa by producing a localized edema and cellular injury of the epithelial lining at and near the site of contact with the pipe stem. Thus, the penetration of the chemical agent into the mucosa may be facilitated.

The alleged causative role of pipe-smoking in the production of this particular type of cancer would account, to a certain extent, for the sex distribu-

tion observed in the general population and for deviations of this ratio in special groups. While the relative incidence of labial carcinoma for unselected series is approximately 10 males to 1 female, von Haberer found this ratio shifted in favor of the women in the Puster Valley of the Austrian Alps, where pipe-smoking is common among women. A similar observation was made in the United States by Pettit and Brewer, who found that labial cancer is more prevalent among Negro women. Pipe-smoking (clay-pipes) is relatively common among Negro females as compared to white females, who rarely indulge in this type of smoking. In a group of white women over 70 years of age, 8.04 per hundred thousand died of carcinoma of the lip, while in a like number of Negro women 30.1 per hundred thousand succumbed to labial malignancy (Brewer).

Additional circumstantial evidence has been supplied by an evaluation of the frequency of lip cancer among the members of various occupational groups, especially disposed to smoking. In a statistical study of the incidence of labial cancer in several occupations, Young and Russell observed that agricultural workers, dock-laborers, outdoor railwaymen, and merchant seamen showed a liability to labial malignancy exceeding by 200 to 300 per cent that noted in the general population. Other outdoor workers, such as masons, general laborers, farmers, graziers, paviours, and similar workers had an excess ranging from 60 to 100 per cent of cancer of the lip. Coal miners working below ground, not being permitted to smoke during work, exhibited a mortality of lip cancer not surpassing that of the average population; in contrast, employees of the mines engaged in work above ground, and having occasion to smoke, showed an excess of labial cancer. Commenting on these observations, Young and Russell expressed the belief that the statistical data supported the conception of causative interrelations existing between smoking, certain occupational activities, and cancer of the lip.

Brief mention may be made of a second habit, common to oriental countries —the chewing of betel, which furnishes an example of the dependence of lip cancer upon an extraneous agent. In a series of 669 cases of betel carcinoma, reported by Orr, 40 affected the lips, while Fells stated that 7.5 per cent of betel cancers were situated on the lips.

III. PHYSICAL AGENTS

The occupational exposure of outdoor workers to sunlight, such as exists for farmers, fishermen, gardeners, trucksters, mail-carriers, and street-cleaners has been blamed by Haagensen for the increased incidence of cancer of the lip in these occupational groups. This investigator stated that the high incidence of lip cancer among outdoor workers has not been recognized. He argued that the location of the cancer on the lower lip, in these instances, was due to the fact that the lower lip protruded and, in contrast to the upper lip, was directly exposed to the carcinogenic action of the sunlight, the labial mucosa thus

exposed containing no protective melanin. Hunt mentioned recently that repeated blistering of the lip by sunlight probably accounts for the high incidence of cancer of the face, including the lip, among the farming population, and for the prevalence of lip cancer in males (98 per cent of total).

Claims have been advanced, blaming various types of mechanical or non-specific, chemical trauma for the development of labial malignancy (Ewing and Pickerill) (scratches, erosion of teeth, contusion, burn and bee-stings). Eggers reported the occurrence of a mixed tumor of the salivary gland type in the upper lip of a man, 69 years old, who had sustained a penetrating injury at this site with a pitch-fork 35 years before. The traumatic antecedent of this type of tumor in the lip is not unique, according to Eggers, as similar cases have been recorded by Pilcher and Mason.

Fischer-Wasels recorded the development of a labial cancer in a man 43 years old, six months following a chemical burn with potassium hydroxide. In the great majority of cases the role of these injuries is purely coincidental; only exceptionally accidental traumas may play a minor contributory or activating part in the causation of labial malignancy.

It is evident from the preceding discussion that cancer of the lip may be caused by occupational exposure to tar, tarry products, or sunlight. It may be elicited by certain carcinogenic agents incident to some habits, such as pipe-smoking and chewing of betel. In medico-legal decisions, concerning the alleged occupational origin of labial malignancy, these causal relations should be kept in mind. They deserve special consideration in regard to the occurrence of lip carcinoma among industrially employed women, as the spread of smoking among women in recent times may be of etiological importance, and the increased use of lipsticks (containing coal-tar dyes) may have an effect upon the future incidence of lip carcinoma in the female sex.

b. The Oral Cavity and Pharynx

1. OCCUPATIONAL ASPECTS

Carcinoma of the buccal cavity, the tongue, and the pharynx is one of the most frequent and fatal cancers among males. This is true, in spite of the fact that these neoplasms belong to the most accessible and most readily recognizable malignant tumors. The relationship of occupational activities to the causation of the oral and pharyngeal newgrowths are strikingly indefinite and uncertain. Young and Russell thought that the statistical data provided some evidence, indicating the greater susceptibility of members of liquor producing and consuming trades to oral malignancy. These investigators and the International Labour Office mentioned, in addition, a number of occupations, which do not seem to have a common occupational factor or a known carcinogenic quality. While Wassink confirmed the greater frequency of cancer of the tongue and pharynx in members of the alcoholic trades (18 per cent in a series of 316 cases of cancer), he asserted that these neoplasms often involved

the base of the tongue and pharynx, while sparing the other parts of the oral cavity. These occupations showed a lower incidence of cancer of the gums, cheek, oral fundus, and tonsils than the general population (2 per cent of oral cancer other than carcinoma of the base of the tongue and pharynx among members of alcoholic trades). Data supplied by the Registrar-General in England suggested that occupations showing an exposure to tar or tarry products exhibited an increased liability to cancer of the mouth. This conclusion is disputed by Peller, who found a lowered incidence of oral cancer among members of these occupational groups. While no information exists concerning the incidence of oral cancer among glass blowers, Darier reported the frequent occurrence of epithelial, hyperplastic and hyperkeratotic lesions (leukoplakias) of the oral mucosa among these workers. These manifestations are regarded as precancerous and are caused by an exposure of the mouth to the mixture of pitch, colophonium, and charcoal, placed by glass blowers in palms of their hands to facilitate the rotation of the hot iron blow tubes. Kennaway pointed out, that 40.8 per cent of all non-scrotal chimney-sweep cancers are found above the stomach (6 in mouth, 3 in jaw, 1 in tongue, 4 in pharynx, and 3 in esophagus) in the alimentary tract, a ratio, which is distinctly higher than that found in the general population (25 per cent).

Since an appreciable percentage (25 to 45) of all oral carcinomas originate from a preceding leukoplakia (Prinz; Stewart; Lane-Claypon; and McCarthy), the factors responsible for the causation of these lesions are of distinct significance and deserve proper consideration in a discussion of the possible etiological, occupational factors of oral malignancy. Leukoplakias of the tongue, formed on the basis of a chronic syphilitic, atrophic glossitis, frequently represent a precursor of lingual cancer. The causal role of an infection of the tongue with trichinella is more doubtful. Trichinosis has only a coincidental part (Gruber; Staübli; and Ewing), for, according to recent investigations, trichinosis is a rather common disease among the inhabitants of the United States (12 to 15 per cent said to be infected) (Pote; and Hall).

II. HABITUAL ASPECTS

Among the habitual exogenous factors related to the genesis of oral leukoplakia and cancer, chronic alcoholism, excessive smoking or chewing of tobacco and betel quids deserve a prominent place (Collis; McCarthy; Ewing; and Eggers). Tobacco cancer of the tip of the tongue in pipe smokers is caused by the chemical action of the tarry distillation products accentuated by heat. Other prevalent sites of tobacco cancers of the oral cavity are the base of the tongue, the palate, the tonsils, and the pharynx (Ewing). Lingual cancers are practically always of the epidermoid type, varying in degree of maturity. Although the tongue contains numerous glands (Weber's mucus glands at the base; Ebner's serous glands near the papillae vallatae; and Blandin-Nuhn's sero-mucus glands at the tip), true adenocarcinomas do not seem to occur, or

are extremely rare, representing a supervention of adenomas of these glands (Bolognesi). Whenever glandular tumors have been observed in the tongue, palate, or other parts of the buccal cavity, they were usually neoplasms resembling the mixed tumor type ordinarily seen in the salivary glands.

In support of the causal significance of these habitual factors, reference is usually made to the sex distribution of oral cancer (male to female ratio is 10 to 1 (Collis; Stewart; and Lane-Claypon)), which is similar to that found in cancer of the lip, for which the identical argument is advanced. It is of importance regarding the etiological relations of exogenous and occupational agents to the causation of cancers, that, in this instance, observations exist, which show clearly the existence of a connection between an exposure to an extraneous, habitual agent and the development of an oral cancer without dependence upon a sex-conditioned, intrinsic factor. The pertinent evidence is provided by another habit cancer of the mouth seen among the betel- or buyo-chewers of the Orient. While oral cancer is rare in white women, this tumor is frequent in Indian women chewing betel (Bashford). Buyo cancer of the oral cavity represents twelve per cent of all cancers among Filipino women (Maxwell; and Vedder). The sex ratio of oral cancer among Filipinos is inverse to that found among white people inhabiting the temperate zones. Davis noted that oral cancer of Filipino women contribute 70 per cent to the total number of cancers of this locality. Variations of customs and habits among the sexes in different oriental countries greatly influence the sex distribution of oral carcinomas. While Bashford noted that cancer of the cheek was found frequently among Indian women chewing betel, Orr reported that, in India, among 669 betel cancers, 83 per cent occurred in men and only 17 per cent in women.

As the available evidence strongly suggests that the occurrence of oral malignancy depends mainly upon the activity of some exogenous and occupational factors, and only to a minor degree upon intrinsic or inherited factors, a brief description of the buyo cancer may be of value, since it is the only environmental carcinoma of the oral cavity about which some definite clinical data exist. The habit of chewing betel or buyo is prevalent among natives of India, Ceylon, Malaysia, Philippine Islands, Indo-China, Siam, and Formosa. The quid consists of Areca nuts (fruits of the Areca or betel palm), slaked lime, tobacco, spices (cardamom and nutmeg), and buyo leaves from the piper betel plants growing in three varieties, into which the other ingredients are wrapped. The green leaves contain about 1.25 per cent of essential oils, while the bleached leaves contain from 4 to 5 per cent of these oils. The betel nut is rich in gallic and tannic acids, which are highly astringent. A red dye is extracted from the nuts by boiling them with lime. This red dye is formed in the mouth from the quid and is responsible for the red discoloration of the oral mucosa. The lime, which is a regular ingredient of the quid, is spread upon the buyo leaf and changes the bitter taste of the leaves into a sweet and pleasant one. The composition of the quid varies in different countries and

districts. There are various species of buyo leaves used, some employed in their fresh, green state, while others are bleached. In Formosa, buyo leaves are replaced by leaves from a local vine. In some parts of India lime prepared from shells is used, while in other regions the lime is made from limestone, which is said to be less irritating than the lime from the shells. Fresh green betel nuts are used in some districts of India, while the dried fruits are employed in others.

These differences seem to have a definite relation to the marked variations in the incidence of betel cancer found in different localities (Snijders and Straub; Orr; Spittel; Maxwell; Degore; Montel; Van Dort; and Davis). The incidence of betel cancer is low in Formosa, Guam, and the Dutch East Indies, where betel chewing is common; but this neoplasm is found frequently in certain districts in India (Madras, Malabar Coast and Travancore), Ceylon, and Philippine Islands. Some investigators attribute the local divergences in frequency of betel cancer to the use of different types of lime (Orr). The lime is not the main cause, as coca chewers of the Andean highlands also add lime to the coca leaves without contracting buccal carcinoma (Eggers). Other investigators attach some importance to the use of green betel nuts, as the cancer rate is high in regions where the fresh nuts are used.

It is possible that these variations in cancer incidence are not related to any differences in the composition of the quids, but are due to discrepancies in habits (Orr). This investigator found, upon an analysis of numerous data, that people in regions with a high betel cancer rate kept the quids in their mouths many hours at a time for economic reasons, thus establishing a prolonged contact of the oral mucosa with an irritative agent. In districts with a low betel cancer incidence the population is on a higher level economically, and quids are renewed at more frequent intervals. While the primary or principal cause of betel cancer is still unknown, no doubt exists as to the carcinogenic significance of the habit, despite the fact that only a small percentage of the large number of betel chewers develop ultimately a carcinoma of the buccal cavity. Approximately 90 per cent of the elderly individuals of the Philippine Islands are betel chewers.

The causal significance of this habit in the production of oral cancer is indicated by the fact that carcinomas of this site represent an appreciable portion of the total number of malignancies. Fells found in Southern India that 91.5 per cent of all cancers observed (377 cases) were buccal carcinomas. Snijders and Straub noted, among a collected series of 1,700 carcinomas of all sites, 653 cases of oral cancers (38 per cent) in Travancore, while the percentage of oral tumors was 42.1 in Madras (411 out of 976 cancers of all sites), and 32 in Ceylon (422 out of a total of 1,325 cases). Bentnall stated that in southern India, 34.9 per cent of all cancers were located in the oral cavity. The exogenous causation of this cancer occurs at a much earlier age than oral carcinoma is usually seen. Bentnall asserted that betel carcinoma occurs at an age averag-

ing 20 years younger than the cryptogenic type in Great Britain. This is not an observation made in all oriental countries concerned, as other investigators noted that the average age is 52 years, although the tumor may attack young persons (23 years old) as well as very old ones (86 years old). The exposure time may vary from 3 to 60 years; but the average is 35 years.

The most frequent site of the betel cancer is the inner aspect of the cheek on the buccal mucosa opposite the molars and pre-molars, where ordinarily the quid is carried. Nevertheless, other parts of the oral cavity may be affected [cheek: 296 cases; lower jaw: 196 cases; tongue: 96 cases; upper jaw: 41 cases; lip: 40 cases (Orr)]. The neoplasm starts as an inflammatory thickening of the mucosa, followed by an elevated growth, which later ulcerates. The well-developed, cauliflower-like tumor is stained bright red contrasting vividly with the brown to black-colored teeth. The neoplasm may reach enormous dimensions and perforate the cheek to the outside. In the beginning, mild pains are connected with the tumor growth; but severe, radiating pains are characteristic of the advanced stages. As regionary metastases occur late and very rarely, the patient usually dies from pneumonia or septicemia. The prognosis is unfavorable. The betel cancer histologically is a cornified, squamous-cell carcinoma, originating from the downward growth of the thickened, epithelial lining (Davis).

III. TRAUMA

Chronic traumatism, in the form of defective and ragged teeth or defective and imperfect fillings of teeth, which have pointed or sharp edges or other dental flaws, causing friction and inflammation of the traumatized tissues, has been incriminated in the production of oral malignancy. Despite this, a single, accidental trauma has rarely been recognized as the cause of this condition. The development of a traumatic retention cyst, following a bite of the tongue, was reported by Michon. He observed the formation of a cyst, filled with clear, gelatinous material, several weeks after the accident, and believed that it originated from the local auto-digestion of the tissues of Blandin-Nuhn's gland.

A medico-legally recognized case of traumatic cancer of the tongue was recorded by Hauser. The tumor developed in a scar caused by a caustic burn sustained two years before. Traumatic carcinomas of the mucosa of the cheek were reported by Wainwright and Schabad. In the case record given by Wainwright, an automobile mechanic, 42 years of age, received a blow with a wrench on the cheek, which caused a break in the mucous membrane of the cheek, but not of the skin. Two weeks after the accident a pimple appeared at the site of the trauma, and 8 weeks later a walnut size tumor was found, which proved to be a squamous-cell carcinoma. Wainwright commented that it was hardly believable that a coincidence existed or that a blow called attention to a pre-existing neoplasm. He therefore accepted a traumatic etiology. The case reported by Schabad, also, suggests that a trauma mainly produced a cancer of

the cheek. A soldier, 26 years old, received a gunshot wound through the cheek, which healed without complications. Ten to twelve weeks later a cancer of the oral mucosa was found at the site of the scar.

Of medico-legal importance is a case of lingual cancer in a "pickler" of a storage battery plant. This man had inhaled, during a working period of 10 years, mist, spray, and fumes of sulfuric acid used for the preparation of the lead plates or "grids" for storage batteries. Cancer of the tongue developed. It was claimed that the mist of sulfuric acid caused, upon contact with the tissues of the mouth, a dehydration of cells, associated with functional disturbances and chronic irritation, which resulted in the development of a malignant growth on the basis of an ulcer. The allegation was sustained in court (Workmen's Compensation Acts).

Ameloblastomas, neoplasms of the enamel organ of the teeth, often develop after some injury to the teeth. It is probable that they arise from some part of the odontogenic apparatus or cells with a potentiality for the development of tooth-forming tissues. The primordium may be incited to proliferate by injury, representing one of the several suspected, contributory, causal factors [trauma to teeth or jaw, infection or metabolic disturbances (rickets)] (Eve; Robinson; and McFarland and Patterson). The ameloblastomas are benign, expansive growths located in the jaw, rarely in other sites. They exhibit an unfavorable prognosis, as they tend to recur because of the difficulties of a complete radical removal. Actual malignancy is rare.

IV. EXPERIMENTAL CANCER OF THE ORAL CAVITY

Experimental production of oral cancers has been accomplished by the application of chemical agents, the use of mechanical traumatic procedures, and infection with parasites. Of three rabbits and one dog painted repeatedly with pine tar intraorally, the rabbits developed transient, papillomatous excrescences, while the dog showed, after 88 days, a general eruption of sessile and pedunculated papillomata of the oral mucosa (Kotzareff and de Morsier). The occurrence of oral tumors in mice, receiving applications of tar on the skin, was recorded by Bonne and Koose, who referred this phenomenon to a direct, chemical action of the tar (licked from the skin) upon the oral mucosa.

A chronic traumatic effect of a mechanical nature was incriminated by Stahr for the production of carcinomas at the base of the tongue in rats fed exclusively on oats. This investigator claimed that the hairs of the oats lodged in the papillae vallatae caused a chronic irritative status, which assumed a malignant character. In rats, having a lingual infection with Spiroptera neoplastica, Fibiger found in the majority of animals a glossitis and benign, epithelial hyperplasias. Seven rats thus infected developed, following a chronic desquamative glossitis, true carcinomas of the tongue. The real malignant character of these neoplasms could be demonstrated by their progressive growth and by a successful transplantation for four generations. This observation was confirmed

by Leitch, who stated that an oral infection of Spiroptera neoplastica causes leukoplakia and cancer.

c. Esophagus

There exists little definite information linking the development of esophageal malignancies with certain, well-defined, carcinogenic factors of occupational activities. An excessive liability to esophageal cancer exists for members of liquor producing and consuming trades and for certain types of metal workers (plumbers, brass and bronze workers, tool workers, and electric apparatus makers) (Young and Russell; and Behla and Koble). An analysis of the death rates of various occupations from esophageal cancer led Stevenson to believe that syphilis is a more important factor than alcoholism in the causation of this neoplasm, because, the less alcoholism and syphilis among members of an occupation, the lower the incidence of esophageal cancer.

Consumption of hard liquor, smoking, and eating hot foods contribute to or cause esophageal malignancy. The site of predilection of esophageal cancers at the regions of the normal narrows (level of cricoid; level of tracheal bifurcation, supracardiac region), where ingested material will have the most prolonged and intimate contact with the esophageal mucosa and will exert the most pronounced physical and chemical effect, strongly supports the conception, that exogenous alimentary or otherwise ingested (industrial dusts and vapors) agents play an important role in their etiology. This viewpoint is strengthened by the fact that 75 per cent of all esophageal cancers occur in men, and that 97.5 per cent of these neoplasms are found in individuals over 40 (Schaer). The increasing frequency of esophageal leukoplakias after the age of 40 (in 67 per cent of 237 esophagi studied by Schaer) and the relatively frequent association of leukoplakia and cancer of the esophagus (in 56 per cent of 23 cases) provide additional evidence in favor of this contention. A frequent genesis of esophageal cancers from activated, congenitally misplaced-cell complexes of glandular structure is not likely, as the majority of esophageal carcinomas are cornified, squamous-cell tumors. Esophageal carcinomas are more common in those regions of the esophagus (middle and lower thirds), where such glandular islands are seldom seen.

The occurrence of a traumatic type of esophageal cancer is not recognized by Ewing; Knox; and Hauser; but Fischer mentions several cases in which esophageal malignancy originated from an esophageal scar. Berner reported multiple esophageal and gastric cancers four months after the swallowing of strong ammonia, and Kliment recorded an esophageal carcinoma in an inveterate sulphur eater. Esophageal cancer may be caused by exogenous agents, resulting in anatomical strictures or spastic constrictions of this organ (Teutschlaender). This investigator cited Fleiner for the statement, that the chance of a cancer developing in an esophagus dilated because of a cardiospasm of the stomach was 25 times higher than that of a normal esophagus. Trauma exerted upon the esophagus from the outside of the body is a negligible

factor, as the topographical location of the esophagus protects this organ against the effects of a dull, mechanical force (Kaufmann).

The experimental production of esophageal malignancies was mentioned by Koose and Bonne, incidental to the painting of the skin of mice with tar. Their development was attributed to the ingestion of tar particles licked by the mice from the skin.

d. Stomach

I. Occupational Aspects

The connection existing between gastric carcinogenesis and occupational activities is very slight indeed if judged by the character and quantity of evidence available. Apart from some statistical data indicating an excessive liability to gastric malignancy of certain types of miners [iron, coal, and slate (Young and Russell); iron, lead, and slate (Behla and Koble)], manufacturers of wool and cotton goods (Young and Russell; and Behla and Koble), and workers coming in contact with tar or tarry substances (Registrar General of England and Wales; Peller; and Kennaway), no other information has been placed on record suggesting such interrelations. The contention of Löwy in regard to the excessive occurrence of gastric cancer in cooks on the basis of scars, and in carpenters and weavers due to pressure upon the gastric region during work, is supported insufficiently. This situation must be viewed with serious concern, as the stomach constitutes the most frequent site of cancer in males (approximately 60 per cent of all cancers), and ranks third in frequency in females (about 32 per cent of all cancers), directly following cancers of the breast and uterus.

For these reasons, gastric cancer is the most common type of malignant neoplasm (41.5 per cent all cancers) (Häberlin). The gastric mucosa is exposed to physiological and pathological amounts of physical and chemical traumatization during the ordinary course of alimentation, and comes into frequent contact with numerous substances of noxious character, originating from habitual (smoking and chewing of tobacco, gum, betel, paraffin, and tar, and the swallowing of parts of lipstick) or occupational activities (swallowing with saliva parts of the inhaled, industrial dusts, fumes, mists, vapors, and gases). A plausible explanation for the conspicuous absence of causal relations between an alimentary exposure to exogenous and occupational agents, and the development of gastric cancer is not immediately apparent. A critical analysis of the various factors incriminated in the causation of gastric malignancy is cited, as it is of utmost importance to determine if the lack of occupational causes is attributable to special and unique functional or structural qualities of the stomach, or is a spurious one, resulting from inadequate study.

The occupational contact with tar, crude oils, and similar products has not given rise to any appreciable excessive increase of gastro-intestinal malignancy. A few isolated data point to the possible presence of such interrelations. Southam mentioned that an interesting feature is the development of a skin

cancer and a second primary growth, elsewhere in the body, in mule spinners in England. The stomach, pharynx, and lung are the organs most involved besides the scrotal sac. These extra-scrotal neoplasms appear after the removal of the cutaneous growth. Roesch noted, in a paraffin worker, a triple primary malignancy, involving the forearm, a bronchus, and the stomach. The histological structure of the three carcinomas differed from each other (squamous-cell carcinoma, basal-cell carcinoma, and columnar-cell carcinoma, respectively).

II. INTRINSIC FACTORS

Congenital or hereditary, local, predisposing factors have been mentioned in relation to gastric carcinogenesis. It is not likely that tissue malformations, such as glandular polyps and pancreatic islands in the gastric mucosa, or islands of esophageal or intestinal mucosa displaced into the gastric mucous lining, play any appreciable role as precursors of malignant tumors in this organ. Cancers which are derived from developmental defects or depend upon the presence of hereditary factors occur early in life, as a rule. This is exemplified by retinal neuroblastomas, cerebellar gliomas, mixed renal tumors, suprarenal neurocytomas, and cutaneous carcinomas in xeroderma pigmentosum.

Gastric cancer is a disease of late middle age and of old age. In a large statistical analysis of the age distribution of gastric cancer compiled by Bruckner and covering 22,759 cases, the incidence of gastric cancer in the first three age groups was as follows: 0 to 10 years, 0 per cent; 10 to 20 years, 0.06 per cent; and 20 to 30 years, 1.17 per cent. Similar observations on a smaller series were recorded by Welch; Reiche; and Martin. The average age of an individual afflicted with gastric carcinoma is approximately 60 years. Adenomatoid polyps of the gastric mucosa coexist in only 0.5 per cent of gastric carcinomas (Stewart); and although they seem to represent a predisposing symptom [gastric cancer present in 24 per cent of stomachs with single polyps (33 cases) and in 30 per cent of stomachs with multiple polyps (23 cases) (Stewart)], they are not an important source of gastric malignancy.

Consideration must be given to the fact that congenital, adenomatoid gastric polyps are rare, the majority of these hyperplasias resulting from a chronic inflammatory gastritis. Inflammatory metaplasias are more often the cause of squamous-cell, mucosal islands than congenital misplacements of esophageal mucosa. The absence of gastric carcinoma among the very young, its rarity during infancy, puberty, and young adult life, the lack of a family history of cancer in persons affected during the first three decades with gastric malignancy, and the scantiness of congenital defects in the gastric mucosa indicate clearly that congenital or hereditary, predisposing factors play a minor role in the causative mechanism of this tumor (Bruckner; and Ewing). While the occurrence of a gastric carcinoma in several members of a family has been recorded a few times, the rarity of such observations supports, rather

than disproves, the positive viewpoint taken by some investigators in regard to the significance of hereditary factors.

The claim of Schmidt, concerning the special liability of the constitutionally dynamic type to a gastric cancer in late years, and of the asthenic type to a malignancy in early adult years, has little general significance. There is the possible existence of a racial or dietary factor. Gastric carcinoma is a relatively rare condition in Egypt (Dolbey and Mooro saw one case among 671 cancers during 3 years) and the Dutch East Indies (Bonne observed 1 per cent gastric cancer among all cancers in the Javanese, and 19 per cent in the Chinese living in Java, where a vegetarian diet is prevalent).

III. EXTRINSIC FACTORS

In comparison to these intrinsic factors, the carcinogenic potentialities of extraneous factors of a nutritional, habitual, or occupational nature loom much more prominently. It is true that nutritional indiscretions, a diet deficient in vitamins, chronic alcoholism, and excessive smoking may cause, in some individuals, a chronic gastritis; a condition, in the opinion of Konjetzny and Hurst, causing a glandular, polypous hyperplasia of the gastric mucosa, which ultimately may undergo a local malignant transformation.

Among occupational hazards in this connection, there are gastro-intestinal disturbances commonly observed among dye workers, the gastric ulcer found in lead workers on the basis of chronic arteriolar spasm, and the ulcerative gastritis seen in workers exposed to the inhalation of carbon disulfide (rayon factories and rubber plants) (Audo-Gianotti). The exact degree of the carcinogenic significance of chronic gastritis and peptic ulcer is controversial and uncertain. The coexistence of a polypous gastritis with carcinoma does not prove that the hyperplastic inflammatory condition preceded and predisposed to the gastric carcinoma. The gastritis may represent a reaction secondary to the retention and decomposition of food in the stomach, caused by a carcinomatous obstruction of the passageway. The actual proportion of peptic ulcers undergoing malignant changes in their marginal mucosa is rather small (between 4 to 6 per cent), according to von Bergmann and Hueper. The ulcer carcinoma constitutes only a minor part of the total number of gastric malignancies (6 per cent). When Stewart maintains that 15.6 per cent of gastric cancers studied by him originated from a simple peptic ulcer, the pertinent question may be raised as to whether his post-mortem material may not reflect some unknown environmental factors peculiar to the regions in which Leeds is located.

Stewart's investigations yielded a very significant correlation between the site of a gastric ulcer and its liability to become malignant . . . "whereas only one lesser curve ulcer in 20 shows evidence of malignant transformation, one in every four of those situated in the pyloric canal shows this change." The pyloric region is the location of two-thirds of the gastric carcinomas (Williams), and the lesser curvature is the predominant site of the peptic ulcers

(75-80 per cent) (Stewart; Haynes; and Rodman). Thus, the conclusion can be drawn that the conditions responsible for the production of peptic ulcers and gastric carcinomas, respectively, are unrelated to each other (Bueermann). The great probability of chronic gastric ulcers located in the pyloric canal to become malignant is inherent in the fact that they are exposed in this region to carcinogenic factors. They offer a prepared soil for the action of these agents because of the presence of an epithelial defect, an inflammatory reaction, and regenerative proliferations in the glandular mucosa in the margin of the ulcer. It is scarcely conceivable that simple mechanical friction by food particles, exerted mainly by the churning movements in the pyloric part of the stomach, should be responsible for this predisposition (Hurst and Stewart), or play a major part in it. The topographical conditions and the peristaltic movements of the stomach combine in keeping the ingested material in the pyloric portion of the stomach, and in bringing this part of the stomach into the most intimate, frequent, and prolonged contact with any carcinogenic substances, which might be contained in the gastric contents.

Such a combination of conditions seems to account for the fact that approximately 60 per cent of all gastric cancers are located in the pyloric region. This conception is supported by the great rareness of duodenal cancers near the pylorus, in spite of the fact that ulcerative lesions in this region of the duodenum occur as often as peptic ulcers of the stomach. The fundamental difference in the carcinogenic reactivity between the prepyloric gastric ulcer and the postpyloric duodenal ulcer does not lie so much in a marked discrepancy of the degree of mechanical friction to which these two ulcerative lesions are exposed as in the considerable divergence existing in the time of exposure to potentially carcinogenic agents contained in the ingested material. The validity of this argument is strengthened by the existence of analogous relations between the incidence of cancer in certain parts of the intestinal tract, and the time and intensity of exposure to the intestinal contents containing presumptive, carcinogenic substances, which enter the alimentary tract either by oral ingestion or biliary or intestinal excretion.

IV. TRAUMA

The existence of a traumatic gastric carcinoma resulting from a single accidental injury has not been recognized scientifically (von Bergmann; Borrmann; Ewing; Knox; and Barkmeyer). This negativistic attitude is not always maintained in medico-legal decisions, as under certain circumstances such a causation must be regarded as a possibility. No reliable evidence of any kind exists in support of the contention that a single, acute, traumatic injury to a normal stomach may result in the direct formation of a carcinoma (Boas). The practical application of this dogma encounters great difficulties, as the stomach is an inaccessible organ, and reliable proof of the presence of a normal stomach is not obtainable with the use of the known diagnostic means. The absence of any pre-traumatic, gastric symptoms is without value, as the existence

of peptic ulcers and gastric scars is often discovered on the post-mortem table in individuals, who never complained of any gastric distress at any time during life. The theoretical possibility of an activation of a pre-traumatic gastric ulcer or scar by the accidental injury cannot be excluded entirely in most instances (Gray).

Sufficient evidence exists in support of the claim that peptic ulcers may be caused by traumas to the abdominal wall (von Friedrich; Deitrich; Ebstein; Gray; Eusterman and Mayo; and Crohn and Gerendasy). Several investigators have conceded the possibility that a trauma may cause ultimately a gastric carcinoma through the malignant transformation of a primary, traumatic, chronic, peptic ulcer (Hauser; Ewald; and Kaufmann). In the opinion of Thiem all injuries which may lead to peptic ulcer may cause gastric cancer. Such a development of a traumatic gastric ulcer must be rare (Ewing), as ulcerations of this etiology usually show a rapid tendency to heal (Stern; and Crohn and Gerendasy), and only rarely run a chronic course. A malignant transformation of any of these lesions has not been observed so far (Crohn and Gerendasy; and Stern).

Although these investigators state that the traumatic gastric ulcer cannot be distinguished histologically from the ordinary peptic ulcer, Stern has pointed out that adhesions are present in the traumatic type, suggesting a primary rupture of the muscularis. The persistence of an acute traumatic ulcer and its change into a chronic callous ulcer with secondary malignant transformation can be explained, only by assuming the existence of an additional and probably constitutional factor interfering with the normal, quick-healing process of such mucosal defects. Injuries which may cause gastric ulcers are elicited by the impact of strong, blunt forces to the epigastric region, as, 1) blows from falling bodies (heavy articles); 2) kicks and punches into the gastric region; 3) falls from heights, landing on the abdomen, or striking projecting surfaces; 4) being run over by wagons and automobiles (Crohn and Gerendasy); and 5) chemical burns (Merkel).

Carcinoma of the stomach rarely develops in scars following a chemical mucosal erosion by the action of acids (Merkel). Cases of this type have been reported by Ziemssen and Naumann; Teleky; and Ghon. Alkali burns of the stomach may terminate occasionally in malignant sequelae (Preleitner). Teleky reported a gastric cancer in a man, 22 years old, who had suffered an alkali burn of the stomach 2 years before. A similar outcome of an alkali burn was recorded by Ghon in a child, 13 years of age, the gastric malignancy developing one year after the accident. The tumor originated from the margin of an ulcer located in the lesser curvature.

Additional traumatic, gastric carcinomas were reported by Schad (34 cases); Röpke; Kaufmann; Barkmeyer; Luckow; Stern; and Pauchet and Luquet. The following conditions must be fulfilled, if such claims merit any serious consideration: 1) the trauma must involve the gastric region of the abdominal wall and have been sufficiently severe to have caused actual injury to the

abdominal wall (bruise or contusion) and to the stomach (appearance of gastric distress soon after the accident; bloody vomitus or tarry stools); 2) continuation of gastric symptoms following the trauma until definite evidence of a gastric neoplasm appears; 3) this preparatory interval must last at least six months; 4) the post-mortem examination must show residues of the preceding trauma (old hemorrhages, blood pigments in abdominal and gastric walls, adhesions and splinters or bullets lodged in the gastric wall in or near the carcinoma). If a medico-legal verdict should be rendered, favouring the presence of causal interrelations between the injury and the subsequent neoplastic disease, this decision rests upon probable relations, which are far from certain. The anatomical features of beginning gastric cancers and their general etiology are incompatible with a purely or principally traumatic origin. It may be conceded that an epigastric trauma may aggravate a pre-existing gastric carcinoma (Borrmann; Ewald; and Kissinger).

V. EXPERIMENTAL CANCER OF THE STOMACH

The experimental production of gastric cancer in animals has been accomplished by the use of various agents. Some are identical with those suspected of being operative in the causation of gastric neoplasia in man by occupational exposure (Klein and Palmer).

Tar and Crude Oil. Cancer of the stomach in mice was reported by Bonne following the application of tar to the skin. The percentage of mice developing gastric tumors depended upon the site and duration of tarring. The incidence was highest when the perioral and perinasal region of the skin was painted with tar, affording a greater opportunity for the oral ingestion of this substance. The papillomas produced were single or multiple, carcinomas were rare. Similar observations were made in mice exposed to cutaneous applications of tar by Koose and Cordes; and Walteman. Koose and Cordes believe that these remote effects of tar are not caused by the chemical itself, but by a bacteriophage-like agent, which penetrates the tarred skin and spreads in the body producing cancer in the stomach.

The development of gastric hyperkeratoses and papillomatosis in the forestomach of rats and mice was noted by Buschke and Langer; and Fischer, respectively, following the resorption of tar through the rectum. This conclusion was based on the observation, made by Fischer, that similar changes were found in the stomach of mice when tar was incorporated into the diet. This local intragastric action of tar was confirmed by Schabad and Ménétrier, respectively, who introduced tar into the forestomach of mice and rats, and by Brancati, who found papillomas and carcinomas of the stomach in mice and rats kept on a diet of milk and tar. Rats fed with a mixture of tar, lanolin, aniline oil, and toluylenediamine three to four times weekly developed in one case an adenocarcinoma of the stomach with metastases to the regionary lymph nodes and liver. Other rats of this series showed retroperitoneal sarcomas and myeloid metaplasia of the spleen and lymph nodes (Voronoff and

Alexandrescu). The occurrence of gastric papillomatosis in rabbits, following the intragastric introduction of tar, was recorded by Ishibashi and Ohtani. A similar effect was seen occasionally by Twort and Ing in mice treated with carcinogenic shale oils.

Synthetic Carcinogenic Hydrocarbons. The production of a spindle cellular type of carcinoma in the stomach of rats fed with benzpyrene, dissolved in lard, was reported by Waterman. He observed the development of a carcinoma of the forestomach in a rat which had received orally cholesterol oleate, obtained from a mixture of cholesterol and oleic acid prepared in a vacuum by heating the mixture to 200°C for two hours. Benzpyrene fed as a colloidal solution was ineffective. A negative result was obtained by Ilfeld, who implanted pellets of 1.2.5.6-dibenzanthracene into the gastric wall of rats and mice. Branch commented on the absence of gastro-intestinal tumors in mice painted with dibenzanthracene in spite of the fact that the content of this tract showed a fluorescence indicating the presence of the chemical.

Otsuka succeeded in the production of a gastric papillomatosis in rats kept on a diet containing diazoaminobenzol. The tumors occupied the fundus, were not malignant, and appeared in eleven rats surviving for more than 11 months while being on this vitamin deficient diet. These observations were confirmed by Sasaki and Yoshida, who likened the gastric papillomatosis of the rats to that observed by Fibiger following the infestation with Spiroptera neoplastica. Van Prohaska, Brunschwig, and Wilson obtained 2 papillomas in the stomach of 48 mice fed with methylcholanthrene. Waterman reported squamous-cell carcinomas in the gastric mucosa of 5 out of 6 mice receiving oral administrations of benzpyrene. Kinosita reported that the oral introduction of 4-oxyazobenzene and of 4:4′ tetramethyldiaminobenzophenone into rats resulted in the formation of gastric papillomas, while the action of 4:4′ tetramethyldiaminodiphenylmethane was less pronounced.

Numerous attempts made by other investigators to produce cancers of the stomach by the oral introduction of carcinogenic chemical agents ended in failure (Reinhard and Candee; Oberling, Sannié, Guériné, and Guérin; Stewart; Cook, Haslewood, Hewett, Hieger, Kennaway, and Mayneord.

Recently, Stewart and Lorenz caused squamous-cell cancers of the stomach in mice, by the oral administration of such carcinogens. The production of malignant, gastric neoplasms by the direct injection of the carcinogenic agent into the wall of the stomach gave positive results in several instances, showing the neoplastic reactivity of the gastric tissues to these agents (Stewart; Rusch, Baumann, and Maison). The production of cancer and precancerous, hyperkeratotic lesions in the forestomach and pyloric region of rats fed with appropriate amounts of pure sulfur and cholesterol was claimed by Tanaka. Klein and Palmer concluded from an analysis of the literature that there does not exist a single, well-established case of an adenocarcinoma of the stomach produced experimentally.

Aluminum. The alleged connection between an exposure to aluminum and

gastro-intestinal cancer (Odier; Held; Editorial, Jour. Am. Med. Ass.) has been investigated experimentally by several workers with negative results (Bertrand and Serbescu; and Reif). In the experiments conducted by Bertrand and Serbescu the ears of rabbits were painted with tar, while aluminum sulfate was administered daily directly into the stomach of these animals (daily dose equivalent to 20 mg. metallic aluminum). There was a cancerous response on the ears, but the post-mortem examination showed an absence of any neoplastic reactions in the gastro-intestinal tract. Similarly negative results were obtained by investigators of the Reichsgesundheitsamt, who fed dogs with appreciable amounts of aluminum salts over an extended period. Myers and Mull could not demonstrate the presence of aluminum in human cancer tissue. The occupational inhalation of aluminum dust which may cause the development of a pulmonary aluminosis, is not complicated by neoplasia of the lung or stomach (Report, Lancet; Doese; Filipo; and Feil). The evidence on hand does not support the contention of a carcinogenic action of aluminum and its compounds.

Radioactive Substances. Daels and Biltris recorded the occurrence of a gastric adenocarcinoma in a guinea pig 19 months after the intraperitoneal implantation of a glass seed containing radium.

Parasites. The observation of gastric carcinomas in several wild rats infested with a small nematode, Spiroptera neoplastica (Gongylonema neoplasticum) led Fibiger to his alleged, experimental production of malignant tumors. In these investigations, rats infected with Spiroptera neoplastica contained adult worms in the squamous epithelial mucosa of the tongue, esophagus, and forestomach. The eggs produced by these nematodes are excreted with the feces, which, when eaten by a certain type of cockroach (Periplana americana), develop into free embryos in the body of their hosts. The embryos invade the striated muscle and become encysted. When these infected cockroaches are eaten by rats, the embryos are liberated from their shells and burrow as larvae into the squamous epithelium of the stomach, where they mature into adult worms. In reaction to these parasitic invaders the squamous epithelium of the forestomach develops papillomatous proliferations.

The degree and character of this epithelial growth response varies with the extent of the parasitic infection. There is only a minor thickening together with an inflammatory reaction if a few nematodes have become embedded in the mucosa. Huge, multiple, papillomatous masses are found, when a massive invasion of the epithelial lining of the forestomach exists. The submucosa shows a marked chronic inflammation. Six weeks to three months after the infection these epithelial proliferations exhibit infiltrative growth. Epithelial-cell strands extending into the muscularis indicate the malignant character of these papillomatous excrescences. This type of development is observed in approximately 50 per cent of the rats surviving the infection for more than six weeks. Metastases occur in the regionary lymph nodes and in the lungs.

White mice are less susceptible by far to this infection than rats. Only 5 to 6

per cent of infected mice develop gastric neoplasms, which may involve the glandular portion of the gastric mucosa and give rise to the development of adenopapillomas and papillary adenocarcinomas (Leitch; and Joannovič). The causative mechanism operative in the production of these tumors represents a controversial subject. During the early developmental stages of these neoplasms, a direct quantitative relation exists between the number of infecting parasites and the degree of the epithelial proliferative response. Fibiger; and Stewart have maintained that the neoplasms are the result of a toxic action exerted by the worms upon the surrounding epithelial cells. Borrel believed that the worms harbor a carcinogenic virus, which they convey upon the epithelial cells lining the forestomach of the rats. This conception implies the presence of a high specificity of the hypothetical virus. It must display not only an organ specificity, but also a cell specificity, as only squamous-cell tumors are formed in the rats. A plausible reason for the lack of this cellular specificity, when the virus is present in the stomach of a white mouse, has not been advanced as yet. It may be mentioned that Passey, Leese and Knox; and Bullock and Rohdenburg repeated the experiments of Fibiger and were unable to obtain gastric lesions of the type observed by this investigator.

Another nematode (Capillaria hepatica), living parasitically in rats (M. norvegicus), may give rise occasionally to gastric cancers (carcinomas and sarcomas) (Beatti; and Bonne). The experimental reproduction of these tumors was accomplished by Vogel, who obtained squamous-cell carcinomas in the stomach of black and white rats fed with mature ova from this worm.

Bonne and Sandground recently reported the spontaneous occurrence and experimental production of glandular papillomas bordering, in part, on malignancy in the stomach of macacus mordax, by intramucosal infestation with the nematode Nochtia Nochti.

Parasitic infections are of little or no practical significance in regard to the etiology of gastric malignancy in man. They are of great importance concerning the controversial fundamental aspects of the character of causative agents and causative mechanism operative in the production of cancer in general (nonspecific chronic irritation, specific chemical agent produced by the parasite, virus contaminant, and tissue, organ, and species specificity of the neoplastic response) (Hoeppli).

e. Intestine

I. Occupational Aspects

The information regarding the existence of causal interrelation between occupational activities and neoplasia of the intestinal tract is more scanty and uncertain than that cited in connection with gastric cancer. Men engaged in sedentary work and disposed to constipation and auto-intoxication are predisposed to intestinal tumors, according to Young and Russell. Peller contended that persons with occupational contact with tarry substances show an excessive

liability to intestinal cancers. This paucity of exact and reliable knowledge is disconcerting.

The intestinal mucosa comes in contact with various exogenous, noxious agents contained in the ingested matter and with numerous, extraneous, toxic substances which, having entered the body through the skin, respiratory organs, or mucous membranes of the upper portions of the alimentary tract, are excreted into the intestine with the bile. There is ample opportunity for different occupational, extrinsic factors with known carcinogenic qualities to exert a neoplastic action in the intestinal tract. It must be conceded that the complex conditions prevailing normally in the intestine interfere greatly with an unequivocal demonstration of these postulated interrelations.

As intestinal cancers constitute from 9 to 12 per cent of all malignancies, a detailed and extensive study of the etiology of these tumors is an urgent necessity and of great practical and scientific importance. The present efforts must be restricted to a critical analysis of the information already available concerning the causation and the causative mechanism of these tumors. The data thus obtained lend a certain amount of support to the supposition concerning the etiologic role, which exogenous factors may play in the production of intestinal cancers (Feyrter; and Oberndorfer).

II. DISTRIBUTION AND CAUSATIVE MECHANISM

If the numerical distribution of the precancerous and cancerous lesions upon the various portions of the intestinal tract, the topographical relations, and the respective lengths of the parts are studied, certain data point to the action of some definite physical and functional factors, determining the sites of the occurring growth manifestations. The following compilation may illustrate the existing correlations:

LENGTH OF INTESTINE AND INCIDENCE OF CANCER

Part	Length in Meters	Incidence of Cancer
Intestine	7.5 –9.00	9.0–12.0 per cent of all cancers
Small intestine	5.5 –7.00	2.5–10.0 " " " " intestinal cancers
Duodenum	0.27–0.30	2.0– 5.0 " " " " " "
Jejunum-Ileum	5.20–6.50	0.5– 7.0 " " " " " "
Large intestine	1.50–2.00	90.0–97.5 " " " " " "
Caecum-Colon	0.75–0.93	30.0–35.0 " " " " " "
Sigmoid	0.52–0.57	20.0–25.0 " " " " " "
Rectum	0.12–0.15	40.0–45.0 " " " " " "

An incidence curve of intestinal cancers, which starts with a low point in the region of the duodenum, shows a marked drop in the region of the jejunum-ileum. This is followed by a steep and constant rise in the region of

the large bowel, and attains a high peak at the end, in the region of the rectum. The incidence of cancer in the various parts of the intestine is entirely unrelated to their lengths (i.e., the surface area). The distribution of the intestinal cancers does not depend upon the relative surface area of a particular part of the intestine coming in contact with the substances present in its content.

The nature of the controlling factors becomes clearer when the distribution of the tumors within the individual parts of the bowel is studied. Of the 2 to 5 per cent of intestinal cancers occurring in the duodenum, 60 to 80 per cent are situated on or near the papilla Vateri, where the bile and pancreatic secretion enters the duodenum. The next most frequent location of duodenal malignancy is the parapyloric region. The infra-ampullary zone exhibits the lowest incidence of tumors [Fenwick: 51 cases of duodenal cancer: 21.5 per cent, supra-ampullary (para-pyloric) location; 57 per cent, periampullary (region of papilla Vateri) location; 13.5 per cent, infra-ampullary location. Geiser: 71 cases of duodenal carcinoma: 15.5 per cent, supra-ampullary site; 71.8 per cent, periampullary site; 12.7 per cent, infra-ampullary site. Rolleston: 40 cases: 20.0 per cent, supra-ampullary location; 60 per cent, periampullary location; 10 per cent, infra-ampullary location]. The supra-ampullary location of duodenal cancers, chiefly near the pylorus, agrees with the distribution of duodenal ulcer (Ewing), and reflects the etiological relations apparently existing between the two conditions (Jefferson). The ulcer craters or cicatricial, duodenal diverticles may retain traces of the carcinogenic material included in the gastric content, when this material is emptied into the duodenum, or may come into contact with cancerous matter excreted with the bile, and regurgitated into the duodenal bulb. Such a retention may be accentuated by the presence of adhesions or spasms.

The accumulation of duodenal carcinomas on and around the papilla Vateri is a clear demonstration that carcinogenic substances are excreted under proper conditions with the hepatic secretion. Corresponding to the increasing dilution of carcinogenic matter contained in the bile by the duodenal contents, the incidence of malignancy decreases rapidly beyond the periampullary section of the duodenum. The relatively quick passage of the chyme through the small intestine decreases an effective contact of any carcinogenic substances which may be present in this material with the intestinal mucosa. Carcinomas of this part of the bowel are relatively rare because of this. The great majority of malignancies of the small bowel are situated in the prececal portion of the ileum, that is, where the chyme moves less rapidly through the intestinal conduit than in the upper portion, and thus establishes a somewhat longer contact with the intestinal mucosa.

Similar conditions determine the incidence and distribution of cancers in the different parts of the colon. Here the intestinal content, by re-adsorption of most of its watery components, is concentrated and the movement of the fecal matter is much slower than in the small intestine. An increased oppor-

tunity is afforded for any carcinogenic substances, possibly contained in the digested material, to exert their specific action upon the mucosa. Such an effect should manifest itself most in those parts in which the fecal matter moves very slowly or remains stationary for prolonged periods, depending upon the normal or pathological functional status of the bowel (spastic or atonic constipation). These considerations provide a plausible explanation for the considerably higher frequency of cancers in the large intestine compared with that in the small intestine, and for the relative distribution of these tumors in the different parts of the large bowel. The incidence increases rapidly with the approach to the anus and is highest in the sigmoid and the rectum (Körte; and Petermann and Anschütz: 297 colonic carcinomas: 47 in cecum; 22 in ascending colon; 19 in hepatic flexure; 44 in transverse colon; 31 in splenic flexure; 10 in descending colon; 124 in sigmoid. Kaufmann: 123 carcinomas of large bowel: 36 in colon; 28 in sigmoid; 51 in rectum).

The hemorrhoidal area of the anal region, with its sluggish blood supply, does not create a favorable soil for the development of rectal malignancy (as contended by Behan). On the contrary, rectal hemorrhoids figure rarely in the carcinogenesis of this part of the bowel (Ewing; Kraske; and Hayden and Shedden), in spite of the frequent irritation and injury to which the anal region and the protruding, hemorrhoidal nodes are exposed. A similar parallelism exists between the functional dynamics and the distribution of tumors in regard to the urogenous tract, in which the ureter takes the place of the small intestine, and is rarely the site of neoplasia.

III. PRECANCEROUS LESIONS

Congenital Polyposis. Several aspects of the developmental history and the local distribution of certain intestinal, precancerous lesions, the polypous adenomas, are in accord with the conceptions developed, regarding the factors controlling the causation and localization of intestinal malignancy. Intestinal, adenomatoid polyps are uncommon during the first decade and are usually single during this period (Erdmann and Morris). They become more frequent in the following decades and are then often multiple (Hullsiek; and Fansler). The age distribution of a series of 93 cases was as follows (Hullsiek):

Years:	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Cases:	5	23	21	23	11	4	5	1

While the presence of a hereditary factor was demonstrable in an appreciable proportion of the cases observed (Jüngling; Hullsiek: 11.1 per cent; Schüttler: 17.5 per cent; Döring (1907); Port (1897); Wechselmann (1910); Thorbeke (1914); and Lockhart-Mummery and Dukes (1939): 50 to 60 per cent), the absence of this condition among new-born babies (Feyrter), its rarity during the first decade, and its increase in frequency and multiplicity during subsequent years show rather definitely that these adenomatous pro-

liferations of the intestinal mucosa are not of congenital nature (Feyrter). Intestinal polyps develop as responses to an inherited or acquired special reactivity to some extraneous nutritious agent, or as the result of certain bacterial or parasitic intestinal inflammation (dysentery, tuberculosis, and schistosomiasis).

The causal mechanism present in the formation of intestinal polyps and polyposis displays a great similarity with certain neoplastic manifestations of the skin. Polyposis coli universalis with its innumerable small and large lesions, developing during the early years of life and possessing a congenital or even hereditary background, is comparable to the multiple, cutaneous, proliferative responses observed in individuals suffering from xeroderma pigmentosum. This disease is caused by a congenital hypersensitivity of the skin to the solar rays, and ends as invariably as polyposis coli universalis in a multiple carcinosis of the affected tissue. Polyposis coli, exhibiting solitary or multiple lesions and appearing during more advanced years, corresponds in its causal relation to the neoplastic manifestations appearing in the skin of individuals (farmers and sailors), who have acquired, during the course of a prolonged and severe occupational exposure to the sun rays, a special reactivity and sensitivity to these agents. This results in the production of cellular proliferations, which frequently undergo malignant changes, similar to those seen in the polyps of the colon.

Additional similarities between these two precancerous conditions may be found in the fact that in inherited familial adenomatosis of the colon and rectum, secondary malignant disease appears at an earlier age (30 to 40 years or earlier) than is found with intestinal cancer (rare before 40 years of age) (Lockhart-Mummery and Dukes). The location of the polyps is identical with the generally recognized distribution of carcinoma of the colon and rectum (Lawrence; and Swinton and Warren). Although these investigators contend that adenomatous polyposis of the intestine is the result of a congenital disturbance, they emphasize the fact that these conditions are apparently more frequent than is generally recognized, confirming an observation previously made by Feyrter.

There exists a certain gross similarity of the intestinal polyposis with the papillomatosis of the urogenic tract, which is caused by chemical agents contained in the urine, and a great resemblance between these two conditions in microscopical respects. The early changes of intestinal polyposis are represented by a diffuse glandular hyperplasia of the intestinal mucosa. In this hyperplastic base small microscopic adenomatoid nodules develop, which subsequently protrude and form ultimately pedunculated or sessile, polypous or papillomatous excrescences (Lockhart-Mummery and Dukes; and Lynch and Felsen). These mucosal adenomas exhibit a marked tendency toward a multicentric, malignant transformation (Fitzgibbon and Rankin). Conforming with the postulated, exogenous, carcinogenic causation of intestinal neoplasms the incidence of adenomatous polyposis is much higher in the colon than in the

small intestine (ratio 12:1; Lawrence). The incidence of a malignant transformation of these lesions increases with their nearness to the anus (Erdmann and Morris) (Susman: malignant transformation in 23 per cent of colonic polyps; Yeomans: 40-50 per cent of rectal polyps; and Westhuis: 100 per cent of rectal polyps). The distribution and incidence of intestinal polyposis and carcinoma coincide (Fitzgibbon and Rankin).

In connection with the controversial nature of the problem concerning the causal or contributory carcinogenic factors, it is important to note that especially polyps with a liberal blood supply eventually become malignant (Fansler). The proliferation of the epithelial elements is paralleled or preceded by a proliferation of the vascular elements, according to Fansler, while tumors developing on the basis of an inadequate blood supply remain small or recede into hard, polypous, fibrous nodes. Similar observations, concerning the dependence of the growth of these adenomatous polyps upon their blood supply, were made by Felsen and Wells. Swinton and Warren emphasized the marked vascularity of the intestinal polyps. Proliferation and cancerization of intestinal, adenomatous polyps depends as much upon an adequate vascularization as do the papillomatous aniline tumors of the bladder and the papillary warty, benign, and malignant growths of the skin following exposure to tar. Cancerization occurs most frequently either at the tip of the polyp, where the oldest glandular elements are (Saint), or near the base (Swinton and Warren). They may involve any other portion of the epithelial lining.

Infectious Polyposis. The evidence concerning the carcinogenic tendencies of intestinal polyps associated with and resulting from an infection with Schistosoma mansoni, S. japonica and S. haematobia is controversial. In spite of the fact that schistosomiatic polyposis of the intestine, especially of the rectum, is rather common in Egypt, due to prevalent infection with S. mansoni and S. haematobia, malignancy originating from these polyps is relatively rare (Dolbey and Mooro). This may be due to the fact that during the early developmental stages these polypous formations consist mainly of inflammatory granulomas. It is only during the more advanced phases that they become adenomatous in character and then may represent localized or wide spread adenopapillomata, often of large size (Stewart). Rectal cancer is so rare in Egypt that Ferguson saw only one case in three years, and Dolbey and Mooro recorded seven cases among a total of 671 cases of cancer (1 per cent) (incidence of rectal cancer among European whites: 5.5 to 10 per cent of total cancer rate). These observations of Egyptian schistosomiasis contrast strikingly with Japanese endemic schistosomiasis. Cases of rectal and colonic schistosomiasis associated with rectal or colonic carcinoma have been reported by Fikushima and Kazama. Kazama stated that the incidence of intestinal cancer is higher among the inhabitants of areas infected with S. japonica than among those living outside such regions.

Infectious, ulcerative colitis of bacterial or bacillary, dysenteric or tuberculous genesis with its regenerative, hyperplastic polyposis of the intestinal mucosa rarely furnishes the basis of a malignancy (Swinton and Warren).

Melanosis. Melanosis, a pigmentary disturbance often found together with cutaneous malignancy (solar rays, roentgen-rays, tar, and arsenic), may occur in the colonic and rectal mucosa of very constipated persons using habitually anthracene laxatives (Jacobsen and Klinck; Jacobsen; Bockus, Willard and Bank; and Bacon and Scheffer). While little is known about the exact mechanism of melanin formation, it appears possible that such a synthesis may take place in the intestine given the proper materials and conditions, aminoacids and tyrosinase probably being present (Jacobsen). Pick expressed the belief that the aromatic protein degradation products are absorbed from the large intestine and converted into melanin within the connective tissue by a ferment resembling tyrosinase. The melanin thus formed is accumulated in phagocytic cells situated in the mucosa and submucosa. This melanosis proctocoli is reversible, disappearing within three to six months after the discontinuation of the anthracene cathartics and correction of the constipation. It is not known if the melanosis caused by exogenous agents has any causal relation to malignant developments occurring in this organ.

IV. TRAUMA

Traumatic intestinal cancers have been recorded by Göckel; Anschütz; Thiem; Löwenthal; Cohnheim; Pometta; Kissinger; Schad; Kaufmann; and Dietrich. It was pointed out by Stern that injury to the intestine by external force is more frequent than that to the stomach. This investigator conceded that trauma may constitute an etiological factor in the genesis of intestinal malignancy. Kaufmann cited several cases of this type which were acknowledged by compensation boards. It seems essential for the recognition of such interrelations that the abdominal trauma must have been so severe that it caused an intestinal hemorrhage. Such an injury may be followed by adhesions or fibrotic stenosis. These may produce conditions in the transportation of the intestinal content, favoring or accentuating the action of preexisting carcinogenic factors. Hauser concluded that an intestinal cancer may be regarded as traumatic, if the presence of an intestinal stenosis or scar formation near the cancerous area can be shown in connection with the history of a severe abdominal trauma.

V. EXPERIMENTAL CANCER OF THE INTESTINE

The experimental production of intestinal malignancy has been accomplished mainly with the use of tar. Genkin and Dmitruk implanted the tip of the appendix of rabbits into the abdominal wall, and painted the appendiceal mucosa with tar through the opened tip. After 41 treatments during a period of nine and half months, one rabbit showed a diffuse hyperplasia of the appendic-

eal mucosa with multiple papillomatous and polypous adenomatoid protrusions. The introduction of tar into the intestine of rabbits resulted in the formation of intestinal carcinoma (Ishibashi and Ohtani; and Leitch). The intrarectal administration of tar into mice by Buschke and Langer; and Schabad did not cause rectal tumors, but was followed by papillomas of the forestomach and, in one instance, a squamous-cell carcinoma of the perineal region.

An important observation was made by Shear in connection with the experimental production of hepatomas in mice by the injection of 2. amino 5. azotoluene. One of the mice treated in this way developed multiple cancers of the liver and an adenocarcinoma of the large bowel. This suggests the possibility that the same chemical agent, which caused the development of the hepatocarcinomas, produced the intestinal malignancy after being excreted with the bile. Recent experiments of Stewart and Lorenz, who fed synthetic carcinogens to mice, resulted in the production of adeno-carcinomas of the intestine which were located most frequently in the duodenum below the papilla Vateri. Twort suggested from his experimental studies with various lubricating oils that substances, present in these agents and exerting an irritation effect on the skin, might cause cancers of the gastrointestinal tract.

Experimental investigations with minerals conducted by Wood were negative. Wood fed pure mineral oil and heavy lubricating oil to 100 mice and 600 rats for three to four months. The rats survived for a year and a half without showing any evidence of gastro-intestinal malignancy.

VI. GENERAL COMMENT

In surveying the various sites and local distribution of cancers in and upon the different sections of the alimentary tract, it becomes evident that these follow certain general rules. These rules are related to the type of causative mechanism operative under the anatomical and functional conditions prevailing in this conduit, and are dependent upon the character of the causative agent and the route of its introduction. The majority of the malignant neoplasms involving the lips and the oral cavity are generally the result of direct contact of exogenous carcinogenic agents with the mucous membranes of these organs. A similar mechanism is responsible for the periampullary cancers of the duodenum, as these are located in an area of intense and primary contact with a carcinogenic agent contained in the bile, and entering the duodenum at the papilla Vateri.

The other predominant sites of cancers of the alimentary tract are determined to a large extent by mechanical moments controlling the passage of the nutritious matter in this conduit, and the duration of exposure of certain areas of the mucous membranes to carcinogenic agents contained in this material. Wherever a slowing of this movement occurs, caused by natural narrows in the canal (esophagus), by sharp and partly fixed flexures in its course, or by a slow peristaltic movement of the bowel (colon and caecum), there are areas

with an increased incidence of intestinal malignancy. This phenomenon is observed in an exaggerated form in places where the ingested material is arrested even temporarily in its passage through the alimentary tract, and where a prolonged contact of this matter with the gastro-intestinal mucosa takes place (pyloric region of the stomach, sigmoid, and rectum). It is in these regions that primary neoplastic multiplicity or even diffuse carcinosis is observed.

f. Liver

I. FUNCTIONAL ASPECTS

The liver constitutes the chief organ of detoxication of the body. Because of this activity numerous exogenous and endogenous substances undergo a more or less radical transformation there. Such changes are accomplished in the liver cells by various means (enzymatic action, hydrolysis, oxidation, reduction, and conjugation). While these alterations in the chemical character of these substances are apt to make them, in general, less injurious to the cells of the body, a reverse action is obtained in some instances. Under these conditions it is obvious that the great majority of carcinogenic materials, with which the organism comes in contact, pass through the liver after they have exerted their specific action or before they have had such an opportunity. In some cases noncarcinogenic agents enter the liver and are transformed by the hepatic metabolism into chemicals with cancerigenic properties. During the course of such multifarious activities the liver cells themselves are frequently injured by endogenous or exogenous poisonous agents. Degenerative, regenerative, and fibrosing changes of the liver are frequent sequelae of endogenous or exogenous poisonings and may lead, in case of a prolonged exposure to toxic agents, to the development of a cirrhosis of the liver. Among the various known or suspected extraneous causes (chemical, bacterial, and parasitic) of cirrhosis of the liver, occupational agents play a prominent role.

II. LIVER CIRRHOSIS AND ITS RELATION TO CANCER

While hepatic neoplasia is not included in any country among the recognized, occupational diseases, the regenerative, adenomatoid proliferations of the liver cells and bile ducts, observed in cirrhosis of the liver, represent frequently precursors to benign and malignant proliferations of these tissue elements (Stewart; Ewing; Tull; and Eggel). This conclusion has been drawn from statistical and histological evidence.

Histological observations reveal proliferative lesions in cirrhotic livers, which represent a variety of changes. They start with simple, multiple, nodular, regenerative proliferations of liver cells or bile ducts, pass through intermediate stages of adenomatoid or adenomatous manifestations (hepato-adenoma and cholangio-adenoma), and end with malignant formations (hepato-carcinoma and cholangio-carcinoma). In accordance with the multiple

character of the benign lesions, there is often a multicentric origin of malignant developments. This suggestive evidence is strengthened by the statistical data demonstrating an excessive coincidence of cirrhosis of the liver and primary carcinoma of this organ.

Eggel found that in 85 per cent of the hepato-carcinomas and in 50 per cent of the cholangio-carcinomas, a cirrhosis was coexisting. In an analysis of 246 primary cancers of the liver, Stewart noted a cirrhosis in 89 per cent of the hepato-carcinomas (219 cases) and in 51 per cent of the cholangio-carcinomas (25 cases). Similar percentages of coincidence were cited by Lipshutz. Cirrhosis of the liver was found in association with primary sarcoma of this organ (Jaffé: cirrhosis present in 15 or 29.2 per cent of hepatic sarcomas). Thus, while not all primary cancers of the liver showed coincidental or causal relations to a cirrhosis of this organ, only a small proportion of the hepatic cirrhoses were found to be complicated by hepatic malignancy at the time of death. However, liability to primary malignancy of the liver is many times higher in a cirrhotic organ than in a normal one.

When the incidence of primary liver cancer was determined in patients with and without cirrhosis of the liver, the following relations were found (Stewart):

		Per cent
Cases without cirrhosis of the liver	7,649	
Cases with primary cancer of liver therein	4	0.052
(with 7 doubtful cancer cases)	11	0.144
Cases with cirrhosis of the liver	264	
Cases with primary cancer of liver therein	9	3.41

According to these figures, the incidence of primary cancer of the liver is 24 times or 66 times, respectively, more frequent in persons, over 30 years old with hepatic cirrhosis than in members of the non-cirrhotic group. This ratio becomes greater, if the lighter cases of liver cirrhosis are eliminated from the calculation. There remain 124 cases with cirrhosis, 9 or 7.3 per cent of them having hepatic carcinoma. Similar relations were deduced by Ophüls, who found 8 cases of liver carcinoma among 126 cases of cirrhosis (6.2 per cent), while in the group without cirrhosis 3 cancers of the liver occurred in 2,111 cases (0.14 per cent) (ratio: 44 to 1). Blumenau encountered, in 12,761 autopsies, 198 cases with cirrhosis of the liver of all grades. In seven instances there was an association with primary carcinoma of the liver (3.5 per cent).

This carcinogenic tendency is not inherent in all types of cirrhosis of the liver. Stewart pointed out that a liver showing a post-necrotic fibrosis with multiple, nodular hyperplasias of the liver cells does not give rise to carcinoma. He reasoned that the acute lytic processes in the liver, produced during an attack of acute poisoning with hepato-toxic agents (arsenobenzol derivatives; quinoline derivatives; aliphatic chlorinated hydrocarbons; aromatic nitro-

compounds and amino-compounds; phosphorus; and arseniuretted hydrogen) are followed, if the patient survives, by a compensatory regeneration of the liver tissue, replacing adequately the amount of liver tissue that has been destroyed. Such livers present a multicentric hyperplasia of liver cells forming rounded nodes of regenerated, functioning liver tissue, separated by broad tracts of fibrosis. There is no distortion of the fundamental lobular pattern. Once the destroyed tissue has become fibrosed and a certain degree of regenerative hyperplasia attained, the lesion becomes static (Stewart).

In the chronic progressive type of cirrhosis of the liver a continuous destruction of liver cells is present, which is followed by a corresponding compensatory hyperplasia of these cellular elements. This process may overstep its bounds and assume the character of an autonomous growth (Muir). The agents, which bring about such alterations, must act, according to Moon, repeatedly and continuously causing the production of diffuse chronic hepatitis. This is indicated by degeneration and necrosis, by regeneration of parenchyma, and proliferation of connective tissue. If injury to the liver parenchyma is severe, continued, and repeated, the repair will be accompanied by fibrosis (Moon). The reparative process does not result in the formation of the ordinary lobular pattern under such conditions. It takes on the form of nodular formations following the type of circulatory disarrangement, which causes the distortion of the architecture of the cirrhotic liver (Laennec's type). Cirrhosis of the liver associated with hepatic siderosis and hemochromatosis belongs to this group of hepatic fibroses, which exhibit a tendency to subsequent primary malignancy of this organ (Stewart). This investigator observed in a series of 151 cases of hemochromatosis, collected from various sources, 15 cases of hepatic cancer (9.93 per cent).

From this rather well-established interrelation between cirrhosis and primary carcinoma of the liver, it may be deduced that some of the causative exogenous agents operative in the production of hepatic fibrosis are directly or indirectly responsible for the development of hepatic malignancy. This carcinogenic effect represents a direct action of a carcinogenic component in the cirrhotic agent upon the liver cells, or the cirrhotic process results in the development of metabolic disturbances in the liver function, which give rise to the production of endogenous carcinogenic agents.

Since no information exists in this respect for the majority of known, exogenous cirrhotic agents with possible occupational significance, it is necessary to list and discuss briefly the various cirrhosis-producing factors whether they have shown carcinogenic qualities or not. Although proof of the cirrhosis-producing properties of many of these agents is based on experimental evidence, an occupational or general environmental exposure to a great number of them can be demonstrated. In fact, there exists a limited amount of casuistic information supporting the actual occurrence of cirrhosis of the liver of industrial etiology.

III. ETIOLOGY OF LIVER CIRRHOSIS

Inorganic Chemicals

a) Phosphorus. The acute necrotizing effect of large doses of yellow phosphorus upon the liver cells is well-known from human cases af acute phosphorus poisoning, characterized by severe yellow atrophy of the liver. Nevertheless, small amounts of yellow phosphorus administered over a prolonged period to rabbits and dogs may cause a pronounced perilobular fibrosis with degeneration of liver cells in these animals (Wegner; Dinkler; Krönig; Ackermann; Aufrecht; DeJosselin de Jong; Fischler; Tischner; and Mallory). There is no appreciable distortion of the lobular pattern or disturbance of the vascular arrangement. Phosphorus may be responsible for the occurrence of hepatic cirrhosis in drunkards, as Mallory surmised that phosphorus might contaminate spirituous liquors by an acid erosion of iron and tin-plated vessels, releasing phosphorus. The tests made by Mallory for phosphorus in 25 spirituous liquors, however, were negative. The evidence in support of an etiological significance of chronic phosphorus poisoning in human cirrhosis of the liver is very doubtful, and the cirrhosis produced experimentally in animals does not follow a pattern characteristic of Laennec's cirrhosis. Consequently, an occupational exposure to phosphorus does not seem to play any causal role in the production of primary carcinoma of the liver.

b) Arsenic. The acute hepatotoxic effect of organic and inorganic arsenicals is well-known from the occurrence of acute yellow atrophy after the administration of arsphenamine, and the inhalation of arseniuretted hydrogen. Chronic arsenic poisoning of environmental or occupational nature may result in the development of cirrhosis of the liver [observed in individuals using arsenicals as parasiticides in agriculture (vineyards), and in persons living near fields and vineyards treated with arsenicals or consuming agricultural products contaminated with these chemicals (Schöndorf)]. Over 80,000,000 pounds of arsenicals (lead arsenate and copper arsenate, principally) are used yearly on fields, orchards, lawns, and trees in the United States alone, and considerable amounts of these chemicals are employed for the same purpose in all other civilized countries. Consequently, the possible hazard of chronic arsenical poisoning is actual for large portions of the general population. The liver constitutes one of the chief storage places of arsenic in the body (Underhill; Osborne, Putnam and Hitchcock). The liver cells may contain arsenic in a crystalline form in cases of poisoning (Schamberg).

Arsenical cirrhosis of the liver in man has been reported by Geyer; Hamburger; Reynolds; Sturrock; O'Leary, Greene and Rowntree; O'Leary, Snell and Bannick; Wier; Dörle and Ziegler; Cannon; and Schöndorf. The arsenic causing these intoxications was contained in drinking water, beer, insecticides, fruits and vegetables, and Fowler's solution.

The experimental production of cirrhosis of the liver by the repeated administration of arsenic was reported by Ziegler and Obolensky; Von Glahn,

Flinn and Keim in rabbits; and Ogata in rats and mice. Variations exist in the degree of susceptibility of the liver of different species to the toxic action of arsenicals (rabbits being more sensitive than ferrets and rats, according to Von Glahn, Flinn and Keim).

The arsenical cirrhosis of the liver seems to be very similar to portal cirrhosis, and represents a type which shows statistically and histologically a certain causal relation to primary carcinoma of the liver. The possibility of such an effect may be likely, in view of the proven carcinogenic properties exhibited by arsenic in the skin.

c) Lead. Chronic exposure to lead, especially in the form of lead arsenate, is likely to cause chronic fibrosing and degenerative processes in the liver; as arsenic and lead exert a hepatotoxic effect. Six cases of plumbic cirrhosis of the liver in man were reported by Lafitte, who reproduced the same condition in rabbits by the administration of lead compounds. Similar results were obtained by Albot in rats, guinea pigs, and rabbits by repeated subcutaneous injection of lead carbonate and lead acetate. The cirrhosis caused by chronic plumbism is of the perilobular type, and not identical with Laennec's cirrhosis. A causal relation to primary carcinoma of the liver is improbable for this reason.

d) Manganese. Manganese compounds have been extensively used for the experimental production of cirrhosis of the liver (Langecker). The subcutaneous or oral administration of manganese salts (manganese chloride and aromatic manganese compounds) to rats, guinea pigs, and rabbits caused liver cell degeneration. Perilobular fibrosis followed resulting in a cirrhosis of the liver of the monolobular, biliary type without appreciable distortions of the lobular pattern (Findlay; Handovsky, Schulz and Staemmler; Martin; Hurst and Hurst; Fiessinger; and Albot). A case of liver cirrhosis in a man with chronic manganese intoxication was reported by Casamajor. It is not likely that this chemical and the hepatic changes it may produce are involved in the causation of primary malignancy of the liver.

e) Copper. A great deal of experimentation has been done to demonstrate a connection between cirrhosis of the liver and chronic poisoning with compounds of copper. The results obtained were contradictory. Mallory, Parker, and Nye claimed that a prolonged feeding of copper acetate to rabbits and rats resulted in the development of a hemochromatotic type of cirrhosis, which was confirmed in regard to rats by Andrianoff and in regard to rabbits by Hall and MacKay. Flinn and Von Glahn; Oshima and Siebert; Herkel; and Schindel were unable to substantiate such findings. In view of the uncertainty of the hepatic action of copper compounds and considering the fact that the cirrhosis observed did not obliterate the lobular architecture, chronic copper poisoning does not seem to have any causal relations to primary hepatic malignancy.

The statement of Moon, that "It seems improbable that inorganic poisons,

with the possible exception of arsenic compounds, constitute an important factor in the etiology of human cirrhosis," is applicable to the causation of hepatic malignancy.

Organic Chemicals

a) Alcohol. While chronic alcoholism is incriminated in the production of hepatic cirrhosis, more recent clinico-statistical and experimental evidence has done much to discredit this conception. The great majority of investigators agree that ethyl alcohol as such, though lacking any cirrhosis-producing properties, may accentuate the action of agents possessing such qualities (Moon).

b) Chlorinated Aliphatic Hydrocarbons (Chloroform, and Carbon Tetrachloride). These chemicals, which are extensively used in industry as solvents, for dry cleaning, etc., are capable of causing cirrhosis of the liver with distortion of the hepatic lobular architecture, if the exposure is prolonged. A case of cirrhosis in man following an occupational exposure to carbon tetrachloride was reported by Poindexter and Greene. Numerous investigators succeeded in eliciting this hepatic response in dogs, rabbits, guinea pigs, rats, and mice after a prolonged exposure to carbon tetrachloride introduced by mouth, inhalation, or subcutaneous injection (Mann; Bollmann and Mann; Lamson and Wing; Albot; Gardner and co-workers; Midorikawa; Smyth and Smyth; Cameron and Karunaratne).

Similar, but not quite so characteristic, cirrhotic lesions of the liver were produced in mice, rabbits, and dogs after the administration of chloroform and tetrachlorethane over extended periods of time (Mertens; Herter and Williams; Fiessinger; Jaffé; Schultz, Hall and Baker; and Macchiarulo). While the occupational exposure to various chlorinated hydrocarbons is extensive, the information in regard to the production of cirrhosis of the liver on the basis of such a hazard is rather meager. The question concerning the possible development of a hepatic malignancy after an industrial contact with these compounds must remain open.

c) Coal Tar. The evidence incriminating tar and tarry substances in the causation of cirrhosis of the liver is almost exclusively experimental. Moon suggested that tar-like products or substances of aromatic character may get into alcoholic liquors, when they are stored for aging in casks which have been charred. Tar-like constituents are formed from the wood during the charring process. Alcohol stored in such casks has a brownish color from the content of such substances dissolved from the semi-charred wood.

Murayama; Schirokogoroff; Leitmann; Davidson; Domagk; and Hu and Wu reported the occurrence of cirrhosis of the liver with destruction of the lobular architecture in rabbits which had received repeated, cutaneous applications of tar for the production of cancer of the skin. Brandt observed a hepatocarcinoma with metastases in a rabbit two years after a series of cutaneous applications

with tar had been made to the skin of the ear. The intraperitoneal injection of carcinogenic shale oil into rabbits was followed by a cirrhosis of the liver of the Laennec's type (Polson). Non-carcinogenic shale oil introduced by the same route proved to be less hepato-toxic.

The evidence in support of a carcinogenic effect of tar on the liver is only of suggestive nature, when taken by itself. It assumes a more definite character, if viewed in the light of observations made with various aromatic distillation products and derivatives of tar.

IV. EXPERIMENTAL PRODUCTION OF LIVER CANCER

Aromatic Chemicals

Matsuo demonstrated that numerous aromatic substances and dyes are excreted through the liver into the bile. Hurst and Hurst; Jaffé; Hueper, Wiley, and Wolfe observed that certain aromatic amines (phenyl hydrazine, aniline, toluidine, and beta-naphthylamine) may cause degeneration of the liver cells and a moderate degree of fibrosis (rabbits, guinea pigs, mice, and dogs). Hueper and his co-workers noted, in their experiments with dogs treated with beta-naphthylamine, that an adenomatoid regeneration of liver cells existed in several dogs without the simultaneous fibrotic changes. Boyland and Brues, with a derivative and possible metabolite of beta-naphthylamine, 3.4.5.6-dibenzcarbazole, showed that this chemical is capable of producing cancers of the skin and hepatomas. Mice treated with this substance first developed a fatty degeneration of the liver cells. This was followed by focal necroses and a regeneration of irregularly shaped and sized liver cells combined with an infiltrative proliferation of bile ducts along the paths of the capillaries. These lesions became diffuse, occupying whole lobules. Their structure became disorganized; groups of abnormally large cells appeared, containing frequent mitoses. Multinucleated, giant, epithelial cells were formed, while there was only a slight increase of the interstitial connective tissue. There were so far no metastases. In addition to these hepatomas, the affected mice showed cutaneous cancers caused by the direct effect of 3.4.5.6-dibenzcarbazole, applied to the skin.

More striking and definite results were obtained by the administration of certain azotized and diazotized derivatives of aromatic amines. Sasaki and Yoshida observed that rats, which fed on a diet of unpolished rice containing o-aminoazotoluol, used industrially as a leather dye, developed a marked proliferation of liver cells without any simultaneous cirrhotic changes. This condition was followed by hepatic adenomas and finally hepato-carcinomas in the majority of rats surviving a sufficient period of time. Cholangio-adenomas and cholangio-carcinomas occurred but were less frequent than the liver-cell tumors (four pure bile-duct carcinomas among a total of 69 tumors in 400 rats).

Hepatomas were obtained in rats when o-aminoazotoluol dissolved in oil was

injected subcutaneously (Yoshida). Nishiyama fed o-aminoazotoluol to mice and found in 6 out of 46 mice thus treated and surviving for more than 11 months, multiple hepato-carcinomas. One animal had, in addition to the hepatoma, a hemangioendothelioma of the liver. A second mouse showed a pulmonary neoplasm. There was hyperplasia of the bile ducts but no neoplastic proliferation of these elements. Shear repeated this experiment, but administered the chemical by repeated, subcutaneous injection into the axillary region (6 times during one year). The first hepatic tumor appeared after 11 months and was single. Liver tumors appearing subsequently were multiple. While tumor formation was not observed at the site of injection, an adenocarcinoma of the colon occurred in one of the mice.

A hetero-organic multiplicity of neoplastic responses to the administration of o-aminoazotoluol was observed by Yoshida, who recorded the occurrence of papillomas of the forestomach and of the urinary bladder in rats besides that of hepatic tumors. Apart from the multicentric genesis of the hepatic, neoplastic reactions of both the liver-cell and bile-duct types, there were frequently hepatic and bile-duct carcinomas in the same liver. The minimal exposure time, by feeding o-aminoazotoluol, was 135 days for rats, according to Yoshida. If the treatment was then discontinued, first adenomas and then carcinomas of the liver (195 days) were formed. The majority of carcinomas increased with the duration of the feeding time and finally reached 100 per cent of the rats treated for more than 250 days. The cancers which arose, after the treatment had been discontinued, seemed to be more malignant than those appearing during the time of treatment. Metastases of the liver tumors were found in the lungs and elsewhere.

Miura and Nishiyama reported separately the production of carcinomas of the liver in guinea pigs fed with unpolished rice and o-aminoazotoluol. Nishiyama noted, moreover, a squamous-cell metaplasia of the thyroid. Leghorn chickens fed or repeatedly injected intramuscularly with o-aminoazotoluol developed, in three instances, adenocarcinomas of the liver after an inflammatory degeneration of the liver cells and proliferation of the bile ducts (Aoji).

While these investigations seem to demonstrate rather definitely the hepatocarcinogenic action of o-aminoazotoluol, subsequent observations suggest that there may exist species specific differences in the neoplastic reactivity to this chemical. Such a response may depend, also, upon dietary factors influencing the hepatic metabolism and, thereby, the chemical character of the conversion products of o-aminoazotoluol in the liver. Yoshida reported that rabbits fed with o-aminoazotoluol developed a cirrhosis of the liver with nodular, regenerative hyperplasias of the liver cells; there was no cancerous reaction.

Heep treated rabbits and guinea pigs for four months with arsenic, preliminary to the administration of o-aminoazotoluol in the food. After 18 months of treatment with o-aminoazotoluol, the rabbits were without any pathological lesions in the liver. Rats subjected to the same type of combined

arsenic-o-aminoazotoluol treatment showed a proliferation of the bile ducts and a dense interstitial, round-cell infiltration (cirrhosis) of the liver, along with an adenomatoid hyperplasia of the liver cells in the central parts of the lobules. Neoplasms were not present in the rats. Heep suggested that the discrepancy between these results and those obtained by the Japanese workers might be due to differences in the vitamin content of the food given (diet of Heep for the rats was bread, turnips, and bacon). Kinosita and co-workers demonstrated later on that the oral feeding of butter yellow elicited hepatic cancers only in animals kept on the nutritionally deficient diet of unpolished rice, while such reactions did not occur in animals fed an adequate diet.

In spite of these negative results with o-aminoazotoluol, there can be no doubt about the hepato-carcinogenic action of this compound, as hepatomas could be produced with several derivatives of o-aminoazotoluol. Thus p-dimethylaminoazotoluol (butter-yellow) when added to their diet, causes carcinomas of the liver of cats (Kinosita). The neoplasms are mainly cholangiocarcinomas. P-dimethylaminoazotoluol is structurally isomeric with the carcinogenic o-aminoazotoluol as well as with the noncarcinogenic p-aminoazotoluol. Yoshida stated that diacetylaminoazotoluol acts like o-aminoazotoluol, but it acts more slowly and requires higher doses than o-aminoazotoluol for the production of hepatic neoplasia.

Some evidence has been advanced indicating that the chemical structure of these chemicals determines to a certain extent, the type of neoplastically reacting cells of the liver. Studying the effect of o-aminoazotoluol, dimethylaminoazobenzol, and a fat soluble fraction of tar, Hashida found that the toluol derivative stimulated the proliferation of bile ducts, while the tar fraction acted upon both cellular elements. A slight chemical modification in the composition or structure of the carcinogenic compounds changed their biological qualities fundamentally. P-aminoazobenzol and p-toluol-p-toluidine (p-aminoazotoluol) elicited hepatic degeneration, while diazoamino-o-benzol was inert (Nishiyama; and Yoshida). Yoshida noted that monoacetylaminoazotoluol and scarlet-red (diazotized aminoazotoluol coupled with beta-naphthol) were ineffective. This was confirmed by Brass, who injected rabbits with scarlet red oil for at least three and a half months after having previously produced a chronic arsenic poisoning in these animals. This investigator observed nodular hyperplasia of the liver with interstitial inflammation (cirrhosis of Laennec), which he attributed to the action of the aromatic amine.

Summarizing the various investigations on the carcinogenic action on the liver of azo and related compounds, Kinosita (1940) recorded the following results: Dimethylaminoazobenzene is strongly carcinogenic, while o-aminoazotoluene is less so; scarlet red and to a lesser degree sudan III, sudan II, toluneazonaphthol, sudan I, and Bordeaux red produce liver adenomas when fed to rats; 4′ oxalylamino 2:3′ dimethylazobenzene and 4′-succinylamino 2:3′ dimethylazobenzene are hepato-carcinogenic in rats; 4:4 tetramethyl-

diaminobenzophenone and 4:4′ tetramethyl-diaminodiphenyl produces hepatic adenomas; and auramine and methyl red exert a mild hepato-adenomatous effect.

Bullock and Rohdenburg injected scarlet red into the liver of rabbits, obtaining atypical, epithelial proliferations and chronic inflammatory changes. They attributed these to a nonspecific stimulation from cellular decomposition products, and not to a direct action of the chemical. Azo-compounds combine readily with bilirubin (Jacobs) and intravenously introduced, carcinogenic hydrocarbons, such as 1.2.5.6-dibenzanthracene, are rapidly excreted in the bile as a water soluble compound (Chalmers and Peacock). Many years previously Schmidt and Korteweg had succeeded in causing hepatic adenomas in mice fed with a mixture of cephalin, olive oil, and scarlet red. Recent experimental investigations of Cook, Hewett, Kennaway, and Kennaway, using a large number of azonaphthalenes and related compounds, demonstrated the hepatocarcinogenic action of 2:2′-azonaphthalene and its reduction product 2:2′-diamino-l—l′ dinaphthyl in mice.

The production of malignant tumors of the liver has been accomplished, also, with the help of synthetic carcinogens of the dibenzanthracene type.

While Claude succeeded in causing a cirrhosis of the liver in rabbits injected weekly with a 4 per cent solution of 1.2.5.6-dibenzanthracene in lard, Andervont obtained in a high percentage of mice, subcutaneously injected with the same chemical, hepatic neoplasms in addition to cancers of the skin and lung.

	No.	*Cutaneous*	*Lung*	*Liver*	*Liver and lung*
1.2.5.6-dibenzanthracene in lard	20	17	1	2	0
1.2.5.6-dibenzanthracene dispersed in dog serum	20	6	6	2	4

The implantation of cholesterol pellets containing 5 per cent 1.2.5.6-dibenzanthracene into the liver of mice was followed in two animals by the appearance of primary liver cell carcinomas.

Woglom tried unsuccessfully to produce liver carcinomas in mice and rats by drawing threads soaked with 3.4-benzpyrene through the livers of these animals. Woglom concluded that the liver of the rat is refractory to the carcinogenic action of 3.4-benzpyrene, as this chemical readily causes the development of neoplasms of the skin in the same animal.

This contention of Woglom is of great general significance, as it is closely related to several important aspects of the causative mechanism active in the development of hepatomas produced by the above-mentioned chemical carcinogens. It is possible that marked species specific variations exist in the sensitivity of certain organs and different tissues to some carcinogenic agents. Such divergences, however, are observed with substances which are most likely not primarily carcinogenic, but which constitute the basis of carcinogenic, metabolic conversion products. As the chemical nature of metabolites of aro-

matic chemicals may vary in different species, depending in part upon their carnivorous or herbivorous characteristics, these metabolic products may possess carcinogenic qualities in some species and not others.

Such variations in the chemical character of the metabolites may account, for instance, for differences in the type of the hepatic reaction to o-aminoazotoluol observed in rats and mice, on the one hand, and rabbits, on the other. Rats and mice respond to the oral or parenteral introduction of this locally non-carcinogenic chemical, developing benign and malignant hepatomas without a complicating or simultaneous cirrhotic process. The same procedure in rabbits causes a marked cirrhosis of the liver without neoplastic sequelae. This observation again demonstrates that there does not always exist the following sequence of events: cirrhosis-degeneration-regeneration-adenoma-carcinoma (Brass). Cirrhosis of the liver does not represent a constant or essential phase in the production of hepatic malignancy (Yoshida). It is doubtful whether the conception held by Wolbach, regarding the genesis of these experimental hepatomas, is correct. This investigator claims that the first change caused by these carcinogenic agents in the liver is a chemical, traumatic degeneration. Necrosis of liver cells is followed by a reactive inflammatory process and a regenerative proliferation of liver cells, from which the neoplastic growth of liver cells ultimately ensues. Investigations of the Japanese workers show clearly that a degeneration of liver cells alone, such as produced by p-aminoazobenzol and p-aminoazotoluol, is not sufficient for eliciting a neoplastic response in the liver. This reaction is dependent upon the presence of a specific chemical factor.

These chemicals pass through the liver cells, as Oppenheimer found that scarlet red was excreted into the bile ducts of mice after oral administration. Similar observations were made by Peacock. Chalmers and Peacock noted that 3.4-benzpyrene injected intravenously is excreted with the bile. These investigators concluded, from the demonstration of small fluorescent globules within the liver cells, that this organ chemically alters the injected hydrocarbon, and the metabolite formed undergoes further changes in the gastrointestinal tract. The concentration of and the duration of exposure to a primary as well as secondary carcinogenic agent must play an important role regarding the production of a neoplastic response in the liver, in view of the fact, that it is an organ which excels in detoxifying properties. These activities are facilitated greatly, if the carcinogenic agent is not only of insufficient quantity, but in addition spread over a large surface (such as existing in a thread), where the prevailing conditions aid in the rapid absorption, dilution, and removal of the carcinogenic agent introduced. This may account for the negative experimental results obtained by Woglom.

Mention may be made of an observation reported by MacNider concerning the syncytial regeneration of liver cells following the action of hepatotoxic substances. This investigator found that the newly formed, metaplastic, re-

generated liver cells exhibited a higher resistance to the toxic agent and displayed a type of cellular, metaplastic immunity of a parenchymatous organ. This conception finds a certain parallelism in the suggestion of Roessle, who noted that cirrhosis of the liver might represent an allergic phenomenon or possess an allergic component. Future investigations must show if reactions of this type play a role in the causation of hepatic neoplasia, elicited by these aromatic substances. Some of the hepatocarcinogenic dyes used produce frequently occupational or environmental allergic dermatoses. This aspect is of great practical importance, as numerous aniline dyes are employed for the coloring of foodstuffs (candies, pastry, fruit juices, fruit preserves, fresh fruits, butter, oleo-margarine, drugs, and cosmetics), and are ingested upon numerous occasions and by the population at large. In consideration of the experimental evidence attesting to the carcinogenic action of certain dyes and intermediaries, Maisin has demanded that the use of dyes for the above-mentioned purposes should be forbidden by law, unless it can be shown beyond doubt that the particular dye used is not carcinogenic.

There does not exist any relation between a susceptibility of certain strains of mice to the spontaneous development of hepatomas and those conferred upon them by a repeated and prolonged injection with aminoazotoluene (Andervont). This observation is of great interest and should be thoroughly checked, as it is in contrast to the effect which this and related chemicals exert upon the initiation and incidence of pulmonary tumors in mice.

Parasitic Infections

Parasitism of the liver plays an important role in the production of the cirrhosis of the liver, especially in oriental and tropical countries, where bacterial, protozoic, and helminthic infections affecting the liver, are prevalent. For this reason these disease conditions are of significance in regard to the genesis of primary hepatic malignancy.

Infections with malarial plasmodia, Endamoeba histolytica, and, to a lesser extent, with Ascarides lumbricoides are responsible for the high incidence of hepatic cirrhosis in Syria and Lebanon, particularly among their rural population (Yenikomshian). Cirrhosis of the liver, etiologically related to bacillary dysentery and malaria, is common among the inhabitants of South India (Menon and Annamalai). Reviewing a series of 54 cases of liver cirrhosis observed in North China, Wang found that syphilis and malaria figure prominently in etiological respects. The causal importance of helminthic infections in regard to the interrelated development of cirrhosis of the liver and primary carcinoma of this organ have been emphasized by Borrel; Lavier; Harant; Strong; and Leitch.

a) Opisthorchis felineus. Opisthorchis felineus is a trematode, which is introduced into man usually by the eating of raw fish, in the meat of which the immature worms are encysted. Its definitive hosts are the dog and cat,

but man may harbor the parasite. The worms lodge in the bile ducts and may elicit a cirrhosis, from which a carcinoma of the liver [in general of the bile duct type (gelatinous adenocarcinoma)] may develop. Infections with this liver fluke in man have been observed in East Prussia, Russia, Siberia, and, occasionally, in China, Indo-China, and India. The presence of worms in the bile passages elicits a proliferation of the epithelial lining, which may be transformed into a malignant growth in the presence of an intense parasitic infection. Carcinoma of the liver in man with this parasitic etiology has been reported from East Prussia by Askanazy; Rindfleisch; and Gruber; and from Russia by Ruditzky; Romanoff; and Ssavinych. Hoogland recorded the occurrence of four cases of hepatic carcinoma and one case of cancer of the gallbladder in cats in connection with distomiasis from Holland, where cats used to be fed on raw fish. As no reliable data exist concerning the incidence of infections with these flukes and their relative association with primary carcinoma of the liver, the evidence supporting an etiological interrelation between these two conditions is not entirely conclusive, but very suggestive. This hepatic neoplasm is, in most cases, the result of an unsanitary habit of eating improperly prepared fish meat. Nevertheless, a certain occupational, contributory factor may enter in the case of the occurrence of these neoplasms among the fishermen in East Prussia, as these men eat raw fish when they are forced to remain at sea for long periods of time because of bad weather.

b) Clonorchis sinensis. Clonorchis sinensis is a trematode, which has as its chief hosts cats and dogs, but which occurs in other carnivores, such as man, rat, hog and, occasionally, rabbit, and guinea pig. The intermediate host is a fresh water fish, usually a carp, in whose muscle tissue the immature worm is encysted. The ingestion of raw, infected meat transmits the infection, which is endemic in certain parts of Japan (up to 60% of population) and China. The worms parasitize in the bile passages and gallbladder. The hepatic lesions are confined originally to the peribiliary regions, where an infiltration with lymphocytes and eosinophilic leucocytes and a proliferation of connective tissue ensue. The epithelium of the bile ducts may be destroyed in the course of this inflammatory reaction or may form adenopapillomatous proliferations (Ruditzky). These may constitute the basis of subsequent malignant transformations. Individual cases of a co-existence of distomiasis and primary carcinoma of the liver have been reported by Katsurada; Yamagiwa; Fuzii; Watanabe; Tsukioka; Watson-Wemyss; Fischer; Bentham; Porter and Pirie; Joyeux; Oldt; Nauch and Liang; and Kabeshima.

Maxwell mentioned that those regions of China, which have a high incidence of hepatic malignancy, are notorious for their high infection with Clonorchis sinensis. This statement cannot be considered as an established fact, as Tull found in South China cirrhosis and carcinoma of the liver frequently associated, but flukes usually were not found. Oldt noted that, among 287 individuals infected with flukes, three cases of hepatic neoplasm

(1.045 per cent) were seen in comparison to five cases of liver carcinoma among 1,461 non-infected patients (0.342 per cent) in Canton. Stewart declared that this difference was not significant statistically.

c) Schistosomiasis. Hepatic schistosomiasis is frequently the cause of cirrhosis of the liver among the inhabitants of South Africa (S. haematobium), Egypt (S. mansoni), and East Asia (S. japonicum). Schistosomiasis intestinalis mansoni has been blamed for the occurrence of hepatic cirrhosis of the Laennec type, and often of the Hanot's variety, among the inhabitants of Venezuela (Jaffé). This parasitic infection of the portal branches by the worms and their ova elicits a periportal fibrosis (Symmers; Katsurada; Fairley; Ferguson; Castellani and Chalmers; Turner and Brebner; Kartulis; and Faust and Meleney).

The type of cirrhosis produced by the infection depends, to a certain extent, upon the severity and the distribution of the parasitic invasion of the liver. A diffuse hepatic infection by a relatively small number of flukes becoming lodged in the portal network, during a comparatively long period, is said to result in the production of a multilobular type of cirrhosis, resembling a hobnail liver. A locally restricted involvement of the portal vessels by numerous organisms is considered as the cause of a periportal type of cirrhosis (Day). Cirrhosis of the liver is associated with the more advanced stage of intestinal schistosomiasis.

The existence of an etiological interrelation between this parasitic manifestation and the occurrence of primary carcinoma of the liver was suggested by Fischer. He stated that an infection with S. mansoni or S. japonicum is often found in cases of primary hepatic malignancy (hepatocarcinoma and cholangiocarcinoma) in South Africa, China, and Egypt. In support of his contention Fischer mentioned the report of Katata concerning the general statistical relations existing in Japan between endemic infections with S. japonicum and cancer of the liver. MacVicar attributed the high incidence of liver cancer in South Africa to the prevalence of schistosomiasis in that country. Individual case reports on the co-existence of schistosomiasis and primary carcinoma of the liver cells or bile duct epithelium were made by Watanabe; Yamagiwa; Kusama (East Asia); and by Mouchet and Fronville (Belgian Congo).

The largest number of cases of this type were recorded by Pirie from South Africa. This investigator studied a series of 36 primary liver carcinomas among African natives (some of them young mine boys, 10 to 15 years old), and found a co-existence with cirrhosis in 31 cases, ten of which could be traced to an infection with S. haematobium. Stewart mentioned that Pirie was unable to confirm his first observations in subsequent investigations. The evidence supporting a causal interrelation between hepatic schistosomiasis and primary carcinoma of the liver must remain of uncertain value, as long as this is not confirmed by observations from Egypt, where the majority of the population is infected by S. haematobium.

d) Miscellaneous Parasitic Infections. In addition to the above-mentioned parasitic infections with definite causal interrelations to primary hepatic malignancy, there exists a number of protozoal and helminthic infections of the liver in man and animals, which have been incriminated in the production of liver cancer upon rare occasions.

Coccidiosis of the liver brought about by an infection with the protozoan Coccidium oviforme, which is frequently found in wild and domesticated rabbits, giving rise to cirrhosis of the liver associated with benign papillary proliferations of the biliary epithelium, was observed upon three occasions in man without causing any malignant growth (Dobell).

Strong cited Jenckel; and Dévé as having observed the co-existence of an ecchinococcus infection and primary hepatic malignancy. While the infection of the human liver by the larval forms of the canine parasite Taenia multilocularis is not rare, its association with liver cancer is extremely unusual, according to Stewart. This author found that there were 32 cases of ecchinococcus infection (0.25 per cent) without co-existing malignancy among 12,800 autopsies. As only an occasional instance of such a combination has been reported (Bamberg; Dibbelt; Necker; Löhlein; and Ziegler (3 cases)), Stewart concluded that a co-existence of ecchinoccocus infection and cancer of the liver is coincidental.

e) Cysticercus fasciolaris. A counterpart to the alleged ecchinococcus cancer of the human liver is presented by the sarcoma of the liver in rats, elicited by infection with cysticercus fasciolaris, and the larval form of the tapeworm of the cat, Taenia crassicollis. The first observation regarding the co-existence of the parasitic and neoplastic disease of the liver of the rat was made by Borrel. Similar observations were reported by McCoy, who found thirteen cysticercus sarcomas at the post-mortem examination of approximately 100,000 American wild rats. Woolley and Wherry noted 3 cysticercus sarcomas among 23,000 American wild rats studied. Bridré and Conseil, who examined 7,700 wild rats of North Africa, found 2,174 infected with cysticercus fasciolaris. Ten of these animals had hepatic sarcomas.

After Bullock and Rohdenberg had established the occurrence of cysticercus sarcoma among laboratory rats, Bullock and Curtis succeeded in producing this tumor experimentally in rats, by feeding them with cat feces containing eggs of Taenia fasciolaris. The neoplasms developed from the connective tissue walls of the parasitic encystments. The incidence of sarcomas depended, according to the subsequent investigations of these authors, upon the severity of the infection. The liability to sarcomatous transformations in the mesenchymatous tissue of the cystic walls increased with the number of cysts present in a particular liver. So far sarcomas have been observed only in connection with this parasitic infection. These highly vascular neoplasms are of spindle cellular structure, showing a tendency toward the formation of multinucleated cells.

f) The recent observation of three cases of hepatic carcinoma in individuals with an infection of the biliary passages with Lamblia intestinalis (Grott), suggest that different parasites harbored by the gastrointestinal tract of human organisms may be causative factors in the development of neoplasms of this tract and its associated glands.

Physical Agents

Radioactive Agents. While the occurrence of hepatic malignancy on the basis of an occupational exposure to radioactive agents has not been recorded, several reports exist on the experimental production of cholangio-carcinomas in guinea pigs caused by radio-actinic energy. Daels and Biltris noted three cases of cholangiocarcinoma in guinea pigs 19 to 30 months after the implantation of radium in glass seeds. After the introduction of 1 microgram of radium into the gallbladder of guinea pigs, Petrow and Krotkowa found a carcinoma of the bile duct epithelium in the liver and precancerous lesions in the mucosa of the gallbladder in one animal. The development of a hepatic sarcoma in one out of five rabbits with intrahepatic implantations of mesothorium was recorded by Uehlinger and Schürch.

V. TRAUMA

The existence of a "traumatic carcinoma" of the liver is not recognized by Ewing; and Knox. This position is justified to the following extent. It is highly improbable from the knowledge available concerning the causation of primary hepatic malignancy that a single and acute trauma to the liver constitutes the main and primary etiology of a hepatic cancer. An acute or a repeated chronic trauma may aid in the preparatory development of a carcinoma of the liver of cryptogenetic origin by producing inflammatory or vascular disturbances in the liver which may stimulate cellular growth. The occurrence of a traumatic hepatic malignancy following within 5 months an acute injury to the liver region was reported by Calcagni. Zahn recorded the appearance of a primary carcinoma of the liver at a site irritated by the friction of a deformed rib. An acute trauma to a carcinomatous liver may aggravate the hematogenous, embolic spread of malignant cell complexes.

VI. RACIAL ASPECTS

The reliable evaluation of the etiological significance of the various factors discussed in relation to the primary malignancy of the liver is impaired and complicated to a certain extent by the fact that cancer of the liver is much more common among the races with a dark pigmented skin, than among those with a light colored skin, whether they are living in their native environment or a foreign one. It is not known definitely whether these variations in the incidence of liver malignancy among different peoples have a racial and genetic origin (pigment metabolism), or are directly or indirectly related to some exogenous, environmental factor of primary or contributory im-

portance (infection, diet, and habits). While Van Dort believes that the differences have a racial basis, others (Bonne) are less certain in this respect, but are unable to demonstrate an extraneous agent. The two colored races excessively affected by primary liver cancer are the Malays and the Bantu (DesLigneris).

A high incidence of primary carcinoma of the liver among the African Negroes was reported by Mouchet and Gérard, who found young males especially affected by the disease. There were 36 cancers of the liver among 163 malignant tumors observed among African natives in South Africa (Pirie). Similar data were supplied in regard to the high frequency of primary liver malignancy in African Negroes by Cazanove; Smith and Elmes; Vint; and Gilman. Chinese and Malays show an excessive frequency of cirrhosis of the liver [6.9 per cent of all Javanese men, 3.5 per cent of all Javanese women, 5.8 per cent of all Chinese men living in Java (Bonne)], and primary carcinoma of this organ, according to Cazanove; Tull; Strong and Pitts; Bonne; Vedder; and Snijders and Straub. (China; Indo-China; Singapore; Java; and California). There were 83 cancers of the liver among 447 malignant tumors (18.6) per cent) found in Java by Snijders and Straub. The great majority of the hepatic neoplasms were present in Javanese and Chinese, where they constituted 57 per cent and 31 per cent of their total tumor rate, respectively. In support of the racial origin of this distribution of liver cancers, Van Dort pointed out that the incidence of these neoplasms is higher among Mongolian races and the Magyars related to them than among those of the Aryan stock; and that Madras peopled by Dravidians shows a high rate, Calcutta and Colombo, inhabited by Aryans, a low rate, and the incidence is again high among the Negroes and Javanese (Stewart).

This investigator presented several compilations which well illustrate the conditions discussed.

TABLE I. RACIAL INCIDENCE OF PRIMARY CARCINOMA OF THE LIVER

Race and Author	Total Number of Autopsies	Cancer of the Liver	Percentage Incidence
English (Hale-White; and Stewart)	31,300	39	0.12
American and Canadian (Clawson and Cabot; Von Glahn and Lamb; Counseller and McIndoe; Ophüls; and Strong and Pitts)	17,736	26	0.146
Hungarian (Goldzieher and v. Bókay)	6,000	18	0.3
Chinese and Javanese (Snijders and Straub; Ophüls; and Strong and Pitts)	1,075	25	2.3
South African Natives (Strachan)	1,100	22	2.0

TABLE II. INCIDENCE OF PRIMARY CARCINOMA OF THE LIVER IN THE FAR EAST

Race	Number of Autopsies	Liver Carcinoma	Incidence
Japanese	12,212	125	1.02
Chinese	1,057	13	1.23
Javanese	658	8	1.22

TABLE III. RACIAL RATIO OF HEPATOMAS TO CHOLANGIOMAS

Race	Total Number of Liver Cancers	Hepatomas	Cholangiomas	Ratio
European and American	176	139	28	5:1
Japanese (Yamagiwa)	42	27	15	
Chinese (Snidjers and Straub; Ophüls, and Strong and Pitts)	36	30	6	
Javanese (Snijders and Straub)	57	56	1	
Negroes (Winternitz; Harvey; and Pirie)	34	32	2	
Total	169	145	24	6:1

There is apparently no appreciable difference in the ratio of hepatomas to cholangiomas among the various racial groups studied. The number of cholangiomas is low among the Malays and Negroes. As the total number of cases is rather small, it is doubtful, whether these figures are significant.

Recent experiments of Des Ligneris with alkaline alcoholic extracts of carcinomatous and noncarcinomatous Bantu livers, subsequently treated with petroleum ether and distilled, showed that such extracts when applied to the skin of mice elicit papillomas and carcinomas (Hieger). No neoplastic responses were obtained with similarly prepared liver extracts of Europeans (Des Ligneris). These results seemed to indicate the presence of a racially conditioned, endogenous, blastogenic substance in the liver of Bantu. Similar studies made by Kleinenberg, Neufach and Shabad; and Hieger, using carcinomatous and noncarcinomatous livers of Europeans, revealed the fact, however, that neoplastic responses can be obtained in mice and rats, following the subcutaneous administration of the extracts of these organs.

g. Gallbladder

There do not exist any known occupational cancers of the gallbladder. Experimental studies of Leitch and Kazama, however, have demonstrated

that the introduction of known, exogenous, carcinogenic agents, such as pitch and tar, are capable of producing infiltrative, glandular proliferations (adenocarcinoma without metastases) within 5 to 12 months after their introduction into the gallbladder of guinea pigs.

h. Pancreas

No cases of occupational cancer of the pancreas are on record. There occur parasitic cysts in the pancreas (ecchinococcus infection), and, occasionally, cancer of the pancreas in connection with a distosomiasis of this organ (Stewart). Two cases of carcinoma of the head of the pancreas occurring in conjunction with a distosomiasis were reported by Romanoff. Trauma to the pancreas may result in the formation of blood cysts, proteolytic cysts, and retention cysts, the latter being caused by cicatricial obstruction of pancreatic ducts (Mahorner and Mattson; and Hueper). Traumatic pancreatic cysts become evident three to five weeks after the abdominal injury, and are seen most frequently in persons between 10 to 30 years old, as the pancreas is more vulnerable in the young than in the old (Honigmann). Cases of traumatic pancreatic cysts were reported by Rose; Snead; Körte; McWhorter; Judd, Mattson, and Mahorner. Körte found a traumatic history (abdominal) in 23 out of 121 cases of pancreatic cysts. Judd and co-workers recorded such data in 8 of 47 cases, and McWhorter stated that 15 per cent of all pancreatic cysts had a traumatic origin.

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[IV]

OCCUPATIONAL CANCERS OF THE RESPIRATORY SYSTEM

1. ANATOMICAL AND ETIOLOGICAL CONSIDERATIONS

THE tissues of the respiratory tract, second only to the skin, come into contact more often and more intimately with occupational agents of various types present in the environmental air in the form of gases, fumes, vapors, and mists or dusts than any other tissue. Moreover the lungs participate in the elimination of extraneous gaseous or readily volatile substances, entering the body through the skin, or the alimentary or respiratory tract, respectively, and contained in the circulating blood. Respiratory diseases of occupational origin represent, therefore, an appreciable portion of the industrial diseases. The nasal cavities and their associated sinuses, the nasopharynx, the larynx, the trachea, the bronchi, and the pulmonary parenchyma may be the sites of these disorders, which vary in type and localization depending upon the physicochemical properties of the different causative factors.

The rapid and extensive growth of industrial establishments in recent decades, the far-reaching mechanization and intensification of the methods of industrial production, the development of many new substances in addition to a considerably expanded use of familiar products for old and new purposes, and the wide spread and highly increased consumption of these industrial products have greatly increased the number of industrial workers and large masses of the general population in contact with industrial products, manufactured goods, and wastes, possessing noxious qualities for the tissues of the respiratory system. This period of large-scale, industrial expansion is characterized by the occurrence of numerous and often new types of inflammatory and degenerative diseases of the respiratory organs, and has witnessed the discovery of a number of new occupational, neoplastic disorders of these tissues. In addition to the increase in the number of cancers of the respiratory organs from these well-established, occupational causes, there has taken place, during this same period of time, a remarkable increase in the incidence of pulmonary cancers of more or less cryptogenetic type. Since this rise in the frequency of cancers of the lung has run parallel to the industrial development of the last four decades, it has been suspected that these two phenomena might have some etiological interrelations.

A number of other non-occupational environmental factors have acted upon the respiratory tissues. The extensive spread of certain habits (cigarette smoking), the wide use of new medicinal products (paraffin oil in nasal and throat

sprays) and medical procedures (roentgen-ray examinations of chest), the occurrence of an epidemic of serious respiratory diseases (influenza and other conditions) introduced during this time, similar important and major environmental changes, thereby creating not only the possibility of a simultaneous causative action of various factors, but introducing also the potentiality of mere coincidence. Some of the extraneous agents, suspected to have been active in the production of the recent spectacular increase of pulmonary tumors, are closely related to or are identical with occupational factors with known carcinogenic qualities. Consequently a detailed analysis and discussion of the evidence available as to general environmental factors is not only of considerable importance for general reasons, but provides an appropriate background for the presentation of the neoplasms of the respiratory tissue of recognized occupational origin.

2. INCIDENCE OF PULMONARY NEOPLASMS

Before the turn of the century malignant tumors of the respiratory system, especially of the bronchi and pulmonary parenchyma, belonged to the rarer types of cancers. The statistical data available from this period confirm this statement.

Author	Years	Per Cent of Lung Cancers in Autopsies
Reinhard	1853–1876	0.057
Weller	1872–1898	0.040 (calculated from 382,671 autopsies reported by several authors)
Fuchs	1885	0.065
Feldner	1852–1879	0.62
	1880–1908	0.90

The incidence of lung cancer prior to 1900, in relation to the frequency of cancer in general, was stated by several investigators to have been approximately one per cent (Ewing; Kaufmann; Pässler; Probst; and Ask-Upmark). After this period there was at first a gradual increase in the frequency of these neoplasms, followed suddenly by a more rapid increase; the gradient becoming constantly steeper during the third decade of this century. The onset of this development varied in different countries and regions. It apparently has reached its peak in some areas [Riga, 1916 (Brandt)], while the increase still continues in others (Fischer). One of the characteristic features of this phenomenon is that it starts simultaneously in different cities, countries, and continents, and shows an increasing continuity over a period of more than thirty years (Peters). This development was not uniform in degree and intensity in the different localities. In Berlin, Hamburg, and Basel the increase was very slow and slight during the first twenty to thirty years of

the century, and has gained momentum only recently. In several cities (or large hospitals) no appreciable changes in the incidence of lung tumors could be demonstrated (Bonser; Passey and Holms; Hanf; Ask-Upmark; Sitsen; Gruber; Breckwoldt; Marchesani; Eichengrün and Esser; and Neely) (Germany: Koelln, Hamburg, Innsbruck; England: Leeds, Glasgow; Sweden: Lund; Russia: Leningrad; United States: Nebraska). The great majority of reports on this subject, based on death certificates, clinical observations, and autopsy findings, note a definite and striking increase of the incidence of pulmonary neoplasms during the last twenty years (Wells; Simons; Weller; Hruby and Sweany; and Hutchison). Autopsy records, which doubtlessly represent the most reliable source of information and which were obtained in large and well-controlled institutions, show this trend of increase in a convincing manner.

The following compilations may illustrate the course of events during the present century:

a) Evidence obtained from death records of the general population.

Bureau of Census (U.S.A.):

Year	*Number of Lung Cancer per 100,000 population*
1914	0.6
1925	1.7
1926	1.8
1927	1.9

Cole:

1901-1910	1.02	for males and	0.70	for females
1931	5.10	"	1.63	"

Stocks (England and Wales):

1921-1930	2.5	"	1.0	"
1933	6.7	"	1.8	"

Kennaway and Kennaway (England and Wales):

1921	361 deaths from cancer of the lung in males
1932	1553 " " " " " " " "

b) Composite data collected from various sources:

Author	*Year*	*No. Autopsies*	*No. Lung Cancer*	*Percentage*
Weller	1872-1898	382,671	159	0.04
	1898-1916	192,271	488	0.24
	1916-1924	33,308	71	0.21
Simons	1900-1930	22,754	137	0.60
	1899 to 1930	from records of 11 American and Canadian investigators		1.55

Simons stated that the same American and Canadian sources showed an increase from 5.88 per cent of all cancer in 1910-1914 to 8.28 per cent in 1925-1928. Similar observations were made by Ask-Upmark on data from

Central Europe. There were 842 cases of lung cancer in that territory during the years 1900 to 1927. In 1900 the incidence of lung cancer in relation to the total number of cancers observed was below 1 per cent, while it rose to 8 per cent for the years 1922-1924. A detailed analysis of the various records, published by a great number of investigators, was made by Hruby and Sweany, who collected records of 185,434 autopsies performed from 1897 to 1933. There were 22,712 cases of cancer in this series, of which 1,355 were primary in the lungs. These workers found that the incidence of cancer in general increased during this period by 65 per cent. At first the increase of lung cancer ran parallel with the general trend, but since 1914 it was higher and, following a temporary decline after 1928, there was a tenfold increase at that time over the incidence at the turn of the century (lung cancers represented 4.1 per cent of all cancers in 1897, compared to 16 per cent in 1928).

c) Data supplied by investigators from individual institutions:

Author	*Years*	*Per Cent of Lung Cancers among Autopsies*	*Country*
Gillespie	1899-1908	0.51	England
	1909-1918	1.64	
	1919-1928	2.91	
Hutchison	1907-1919	0.40-0.93	
	1920	1.07	
	1925	2.05	
Berblinger	1910-1931	0.96	Germany
Wahl	1917-1927	1.12	
Kraft	1925-1932	1.6	Russia
Probst	1906-1910	0.11	Switzerland
	1911-1915	0.38	
	1916-1920	0.59	
	1921-1925	0.97	
Klotz	1910-1927	0.82	Canada
Dissmann	1925-1931	10.85	Czechoslovakia
Materna	1921-1923	8.0	
Holzer	1920-1924	7.98	
Husted and	1914-1918	2.0	Denmark
Biilmann	1919-1923	0.5	
	1924-1928	3.3	
	1929-1932	7.3	
	1933	10.3	
Bonser	1891-1932	6.3-7.5	England
Hutchison	1907	1.0	
	1920-1925	3.1-4.0	
Berblinger	1920-1924	8.3	Germany
Kikuth	1923	9.4	
Hanf	1922-1925	7.5	
Ferenszy and	1914	5.0	

Matolscy	1924	10.3	
Schönherr	1925-1927	11.6	
Junghanns	1918-1922	9.9	
	1923-1927	14.43	
	1925-1927	15.20	
Hueper	1911-1921	10.0	
Seyfarth	1920-1924	8.0	
Wahl	1917-1922	6.06	
	1922-1927	13.01	
Jaffé	1915-1918	10.73	
Simmross	1906-1912	2.5	Germany
	1927-1931	9.83	
Probst	1895-1905	4.01	Switzerland
	1906-1915	3.8	
	1916-1925	4.9	
	1921-1925	7.17	
Staehelin	1924	4.9	
v. Zalka	1919-1923	2.67	Hungary
	1924-1927	6.65	
Jaffé	1935	11.47	United States
Barron	1919-1921	10.0	

These citations do not represent a complete list of investigators who observed and commented on the increase of pulmonary cancers in recent years. It is sufficient to list their names and country, as many of them have been mentioned and the results of their studies reported in Simons' excellent monograph on primary cancers of the lung.

Europe: Denmark: Vosbein; France: Schachter; Doubrow; Vincent; Feil; and Ménétrier; Germany: Sonnenfelt; Brinkmann; Katz; Harms; Lubarsch; Briese; Rau; Riberfeld; Karrenstein; Fischer-Wasels; Oberndorfer; Hegler; Lehmann; Schmorl; Popper; Rogers; and Sitsen; Great-Britain: Duguid; Dunn and White; Shennan; Boycott; Simpson; Maxwell-Nicholson and Hill; Hungary: Haintz; Holland: de Vries; Latvia: Konrad and Franke; and Brandt; Poland: Nowicki; and Syrek; Russia: Prayd; Cabrini; and Wilinski; Sweden: Ask-Upmark; Norway: Hampeln; and Lindberg; Italy: Wackmann; and Carolo.

America: Canada: Klotz; United States: Arkin and Wagner; Fred; Olson; Rice; Bonner; Matz; McCrae; Funk and Jackson; Tuttle and Womack; Menne, Bisaillon and Robertson; Schnurer; Vorwald and Karr; Lemon; Vinson; Moersch and Kirklin; and Rosahn; Cuba: Sierra; Brazil: Torres and de Azevedo; Argentina: Strada.

Australia: Downie; Guttridge; and Cowan and Thomas.

Asia: Japan: Nagayo; and Suzuki.

There cannot be any doubt about the almost universal increase in the frequency of pulmonary neoplasms. An analysis of the data recorded readily shows that marked variations do exist in the incidence of these tumors between various cities and regions of one country and between different countries and continents, which as yet are not explained [Stocks; Bonser (England); Dissmann (Czechoslovakia); and Fischer (Germany)]. It is quite puzzling that pulmonary cancer is rather rare among the inhabitants of Italy (Carolo), not extraordinarily common in France, but frequent among the rest of Europe. Similar discrepancies exist, according to Fischer, in Germany where the lung cancer rate is high in some greatly industrialized districts (Saxony; and Rhineland-Westphalia), but low in some of the industrial regions of northern Germany. Such observations do not permit the conclusion that industrialization does not play any causative role in the increase of pulmonary cancers (Fischer). The existing knowledge of industrial carcinogenic agents is now sufficiently exact and extensive to emphasize the importance of specific agents against the vague conception of nonspecific, chronic, irritative, occupational factors. The lumping together of highly different, exogenous, industrial agencies, such as exist in various mixtures and compositions in any large industrial district, for the purpose of evaluating environmental carcinogenic influences, must result in a confusion of the issue; i.e., unless proper care is taken to compare districts containing the same types of industries working with identical methods and materials and employing approximately an equal number of workers. Plausible explanations will be found for these now obscure divergences, when our methods of analysis of the extraneous conditions existing in these regions have become more intelligent and exact. The increase of cancers of the respiratory tract has not remained restricted to those of the lung. Kennaway and Kennaway concluded, from an analysis of the death certificates of England and Wales, that from 1921 to 1932 laryngeal cancers increased 1.4 fold in males and 1.75 fold in females.

3. SYMPTOMATOLOGY

The diagnosis of lung carcinomas is considered difficult and the correct diagnosis is missed frequently. Several factors are responsible for this fact. First, numerous diseases of the lung may produce symptoms similar to those of lung carcinoma. Secondly, the symptoms caused by these tumors vary considerably, corresponding to the different locations of these neoplasms in the lung, their histological character, proliferative activity, type of local and general extension, secondary changes in the lung as sclerosis, abscess or gangrene formation, and pleural effusion, and metastatic alterations in other organs. In some, no clinical symptoms may be produced during life especially those of the senile type, or the first clinical symptoms do not emanate from the primary focus but from metastases in distant organs, such as the brain and bones. In others, the first and sometimes only symptoms are represented by uncharacteristic pains in the thoracic wall, pains similar to those present in intercostal

neuralgia. These irregularities in the symptom complex of the carcinoma of the lung account for the high percentage of incorrect diagnoses.

a) Subjective Symptoms. Coughing is one of the first and most common symptoms of lung carcinoma. In the beginning it is usually dry, hacking, and may become later productive, especially when gangrenous cavitation of the lung develops. A paroxysmal cough having at times an agonizing or even emetic character is observed in cases where the carcinoma is proliferating in the bronchial lumen.

Dyspnea is, also, an early symptom and present in 90 per cent of the cases (Fishberg). It is caused by the peribronchial and perivascular, carcinomatous infiltration of the lung, producing a rigidity of its tissue and a compression of the alveoli. Dyspnea is aggravated by obstruction of a large bronchus by tumor invasion or by bronchial compression from the outside. Pleural effusion has the same effect. Dyspnea is sometimes an intermittent condition when the mechanical condition of the air passages changes. It may become more severe in the course of the disease and harder to bear. It cannot be relieved by rest in bed. Stridor is rare and occurs only in a late stage.

Pains in the chest are an early and main symptom. They are present in 90 per cent (Fishberg) to 50 per cent (Brandt). They may be continuous or paroxysmal in character. The intercostal neuralgic type is the most common one. They radiate into the shoulder and the arm of the affected side. Pains in the left side may be due to pressure of metastases upon the brachial plexus. Pains in the right costal and lumbar region are caused sometimes by metastases in the liver. The pains become more severe when the patient is lying on the involved side.

Fever is present in only 25 per cent (Brandt) of the cases and due to a secondary infection of the lung by micro-organisms. It is usually of a subfebrile type. High temperatures are present if complications, such as abscess or gangrene of the lung, exist.

Night sweats are observed frequently.

b) Objective Symptoms. Cyanosis and edema of the face and neck are present in 50 per cent at an early stage. Compression of the superior vena cava is responsible for this condition if it is bilateral; compression of the innominate vein produces a unilateral effect. Absence of pulsation in the congested large veins of the neck is produced by thromboses. Sudden attacks of cyanosis accompanied with small, irregular, rapid pulse occur and are caused by cardiac metastases. Superficial ectatic veins appear on the chest, arms, and lateral to the spine in the back. Acrocyanosis and clubbed fingers are observed in 25 per cent (Fishberg). Clubbed fingers appearing in middle-aged persons point to the presence of a carcinoma of the lung. Pressure of the tumor on nerves may result in an inequality of the pupils and paresis of the recurrent nerve (in 6 per cent). Other nervous symptoms may be caused by metastases in the central nervous system.

Cutaneous hyperaesthesia is found in the lumbar region. Palpatory tender-

ness of bones, especially of the ribs and sternum, points to the presence of metastatic growths in these organs. Enlargement of the superficial lymph nodes is rare.

Bulging of the fossae supraclaviculares is occasionally observed. Cachexia represents a condition of the late stage and may be very marked in senile persons, often being the only symptom suggesting the existing malignancy. It is not generally present (Wahl).

Chest findings: The findings obtained by a physical examination of the chest depend upon the character and type of growth. The carcinomas of the lung may be classified from a clinical standpoint into four groups:

1. The pulmonary, nodular, productive type.
2. The pleural type.
3. The pulmonary, disintegrating type.
4. The multiple, small-nodular type.

1. The pulmonary, nodular, productive type is represented by those carcinomas of the lung which form solid, nodular masses, which are the focus for an infiltrative, peripheral growth. On percussion a limited area is obtained which emits a characteristic flat note as found upon percussion of muscle tissue. The pleximeter finger feels a sense of resistance. The area extends either from the inner part of the supraclavicular fossa under the sternum or from the region below the clavicle to the sternum. Breath sounds are absent. These symptoms are produced by carcinomatous infiltration of the lung tissue and atelectasis. They are usually observed on one side only. Tubular or amphoric sounds are heard near the sternum and in the interscapular space originating from bronchi with infiltrated, rigid walls.

2. The pleural type is present in about 50 per cent of the cases. Above the area of complete dullness due to the cancerous effusion a zone is present, which emits a flat note on percussion resulting from the presence of atelectatic and infiltrated lung tissue. Râles are absent in this zone. The fluid often fills the whole pleural cavity. Displacement of the mediastinum is rare, and if existing, it is usually to the affected side. The heart is, in general, in normal position.

3. The pulmonal, disintegrating type is not very common. This form of pulmonal carcinoma is characterized by the formation of cavities due to the disintegration of tumor and lung tissue. Sooner or later there is an abundant, fetid sputum present. Hemorrhages are frequent and high fever and profuse sweating usually accompany this type. The temperature has an intermittent, septic character. The physical findings resemble those observed in abscess or gangrene of the lung. The diagnosis is difficult.

4. The multiple, small-nodular form of lung carcinoma is very rare and offers great difficulties in diagnostic respect. The consideration of the general aspect, such as a rather rapid course, cachexia, and neuralgic pains, and the

results of a roentgen-ray examination may help to establish the correct diagnosis.

A roentgen-ray examination of the chest may show a marked discrepancy between the size of the tumor in the roentgenogram and the extent of the physical symptoms, which are found over a larger area on account of atelectases. The presence of an effusion interferes with the proper interpretation of the lung findings. The effusion has to be removed before the pictures are taken. The establishment of a pneumothorax, which is sometimes prevented by the presence of adhesions, may improve the demonstration of the lung tumor in the roentgenogram. By the injection of iodinized oil into the bronchi, the existence of an obstruction of the bronchi by tumor growth can be visualized. The presence of extensive calcifications in the roentgen-ray pictures of the lung does not support the diagnosis of a carcinoma of the lung.

In the nodular type the tumor appears as an irregularly outlined area of homogeneous density. The density does not increase toward the margin but extends infiltratively into the surrounding tissue. When a whole lobe is affected the consolidation appears as a homogeneous density without any mottling, and is not as marked as that of a fluid. The edge of the shadow is irregular and shows a peripheral infiltration into the healthy parenchyma. Carcinomas originating from the bronchial mucosa in the vicinity of the hilum appear as irregular densities, from which a bronchial tree of increased density radiates. Bronchial tumors may be seen with the bronchoscope in 75 per cent of cases (Jackson and Konzelmann).

Laboratory Findings. The sputum varies in appearance and amount. It may be mucoid, purulent, or sanguinolent. A sanguinolent sputum, which may contain red streaks, be rust brown, or have the appearance of raspberry jelly, rarely is seen early in the disease, while it is present in 60 per cent (Fishberg) of the cases during the late stage. A transitory hemoptysis is more characteristic of primary lung carcinoma than a continuous one. Fat globules, which are indicative of carcinoma of the lung, according to Lenhartz, are found in the sputum in other diseases. Acid fast bacilli may occur in the sputum if lung gangrene complicates the tumor. They are saprophytic bacilli (Muir and Ritchie). A copious sputum usually appears only in a late stage and may be malodorous at times. It originates from cavities.

Effusion: Pleural effusion is present in about 50 per cent of the cases. It may be serous, purulent, or bloody. A purulent fluid is observed in 19.9 per cent and a hemorrhagic one in 29 per cent (Fishberg), but the latter may be transitory.

Blood: A leucocytosis with myelocytes and myeloblasts points to the presence of bone metastases.

Histological examination: The sediment of sputum or pleural effusion can be used for histological examination for tumor tissue. Krampf reported that in one of 26 cases the diagnosis could be made from a histological examination

of the sputum, because only in advanced cases, when larger clumps of tumor tissue are expectorated, this diagnostic procedure may be successful; necrosis and disintegration of the tumor material usually interfere with the success of this method. Fishberg asserted that a correct histological diagnosis was obtained in 70 per cent of the cases from the histological examination of the sediment of pleural fluid. During a bronchoscopic examination tissue may be removed for a histological examination. Sometimes an exploratory thoracotomy, which Lenhartz recommends as a diagnostic procedure as easily done as an exploratory laparotomy, may offer opportunity for the removal of tissue.

4. PATHOLOGY

The gross appearance of the pulmonary cancers depends upon the extrinsic or intrinsic proliferative tendencies of the tumor cells, the site and origin of the tumor, and the unicentric or multicentric development. Bronchiogenic carcinomas exhibit, during the early stages, a polypous character, completely obstructing the lumen of the affected bronchus. During later stages the neoplastic invasion of the adjacent structures converts them into large, irregular masses radiating into the surrounding tissue. This type is found often near the hilum or originating from one of the main bronchi. A second variety of pulmonary tumor, which generally is derived from the peribronchial glands, produces a small primary tumor from which neoplastic extensions spread in the peribronchial tissue. The intrapulmonary, nodular, and rather well circumscribed type originates from a peripheral bronchiole. In very rare cases the epithelial structures of an entire lobe seem to undergo a malignant transformation (diffuse, lobar type) (Kretschmar; Gordon; and Domeny), or tumor growths spring up in many foci scattered throughout the pulmonary parenchyma (multicentric, nodular type) (Helly; Löhlein; Hueper; Oberndorfer; Marchiafava; Malassez; Kitzmiller; Kaufmann; Briese; and Ribbert).

The occurrence of such diffuse or multifocal carcinoses of the lung have been related by some investigators to the existence of congenital anlagen in the lung (Cohnheim theory). However, the sudden appearance of multicentric carcinogenic mutations is not rare in the liver, as a sequela of a cirrhosis (chemotoxic?), and represents a characteristic feature of malignancy of occupational origin without any congenital contributory factor of anatomic nature.

1. Bronchiogenic carcinomas. Their appearance varies with their location near the hilum or, more centrally, in a lobe. The bronchiogenic carcinomas of the vicinity of the hilum are the most common type. They are soft or hard, white or yellow, irregularly delimited tumors, which vary in size from that of a bean to that of a man's head, replacing the normal tissue of a whole lobe. They form a polypous or a papillary node attached with a broad base to the bronchial mucosa. They obturate the bronchial lumen completely, or they show a more diffuse growth converting the bronchus into an eccentric, thick-

walled tube with a stenosed lumen. The latter type is not as common as the former one. Several different types of extension of the tumor into the lung tissue can be distinguished. The carcinoma may extend mainly to the peribronchial tissue using the lymphatics in the bronchial wall, and transforming the bronchus into a thickened, rigid tube. From this tube it may spread into the interstitial tissue in nodular strands which, upon reaching the pleura, form flat, diffuse, extensive, firm infiltrations of this tissue. Sometimes, the interstitial carcinomatous infiltration becomes so dense that the lung tissue is compressed and finally replaced by carcinomatous tissue. The primarily involved bronchus appears as a pedicle of the tumor mass. In a second type there exists a diffuse infiltration of the lymphatics, which form a white, delicate network which crosses the whole lobe and is especially visible in the subpleural tissue. In a third type the tumor spreads diffusely in every direction, forming an irregular mass with the primarily affected bronchus as a nucleus.

In advanced cases the whole lobe may represent a grayish red tumor mass from which, in rare cases, a turbid jelly-like material exudes. Cavity formation follows the blocking or stenosing of the bronchial lumen by the tumor. The blocked bronchial secretion dilates the lumen of the bronchus and secondary inflammatory processes produce an ulceration of the bronchial wall and disintegration of the tumor tissue. The cavity is filled with a gelatinous, mucopurulent or putrid content in which detritus, sequestrated pieces of tumor and lung tissue may be present. Gangrene of the lung is found as the result of an infection with putrefactive bacteria in the surrounding lung tissue. The second type of bronchial carcinoma is more centrally located and starts from one of the smaller bronchi. It forms a well circumscribed, smaller or larger node which sometimes is surrounded by smaller tumor nodules. Central necrosis in the tumor may result in a cyst filled with detritus and pus, which may be emptied by expectoration if perforation of its lumen into a bronchus occurs. This type is rarer by far than the first mentioned one.

In the lung tissue surrounding the carcinoma pneumonic processes are observed. The occlusion of a bronchus by the tumor results in an atelectasis of the corresponding lung tissue with secondary compensatory emphysema of the uninvolved parts of the lung. The emphysema of the healthy lung displaces the heart to the diseased side; unless the formation of an effusion in the pleural cavity of this side prevents this condition, and causes the displacement of the heart to the healthy side. In the course of rapid and marked disintegration of tumor and lung tissue, hemorrhages from eroded vessels occur which may become fatal if a larger vessel is opened.

2. Peribronchial, mucous gland carcinoma produces a diffuse thickening of the bronchial wall, but leaves the bronchial lining intact proliferating mainly into the submucosa. The white or sometimes gelatinous tumor masses cause a stenosis rather than a dilation of the bronchial lumen. Diffuse and extensive infiltration of the parenchyma of the lung occurs as well as marked

sclerosis and contraction of the affected lung. Small cystic formations filled with gelatinous material are not infrequently observed.

3. Alveolar carcinoma occurs in three different types: a single node similar in appearance to the second type of bronchial carcinoma described (Löhlein); multiple small nodules (Marchiafava; Hueper; Malassez; Kitzmiller, Oberndorfer; Briese; and Ribbert); or a diffuse involvement of one or several lobes of the lung (Domeny; Kretschmar; and Gordon). The multiple, nodular type, which may affect one or both lungs, is characterized by grayish, yellow, poorly defined nodules of miliary to hazel nut size, rarely larger. The center of these nodules shows a cheesy necrosis, and the general appearance may not differ from that of a chronic nodular tuberculosis of the lung, especially if a marked fibrosis accompanies the tumor process. In the diffuse type the affected part of the lung resembles a caseous pneumonia or a pneumonic lung in the stage of gray hepatization (Kaufmann). The consistency is more or less firm and in later stages a marked fibrosis may be present, changing the appearance of the tumor tissue to that seen in chronic fibrous pneumonia. In other cases the cut surface may show a certain degree of translucency. A turbid, gelatinous material exudes from the tumor and small cystic formations in the surrounding lung tissue are not rare.

Through continuous growth carcinomas of the lung may involve the pleura, causing an effusion or adhesions with subsequent invasion of the diaphragm, ribs, and other tissues of the chest wall. On its extension toward the mid-line, the carcinoma may spread directly into the peribronchial lymph nodes and those at the hilum, into the mediastinal tissue compressing the superior vena cava, into the pericardium, and after perforation into pulmonal vessels into the heart (left auricle). Discontinued growths are usually very numerous and widely spread on account of the ready invasion of the dense network of blood and lymph vessels of the lung. But there exist great variations corresponding to the degree of malignancy of the carcinoma. Lung carcinomas of old persons occasionally produce no metastases, but remain small and localized and are accidental findings at autopsies. Metastases are absent in about 10 per cent of all carcinomas (Ewing). Probst saw metastases in 81.6 per cent of his cases, Seyfarth in 75 per cent, Bilz in 88.9 per cent, and Redlich in 96.6 per cent. The organs grouped according to the frequency of occurring metastases are as follows: Liver, lung, pleura, bone, kidney, adrenal, brain [35 per cent (Fried)], pericardium, heart [1.3 per cent (Kikuth)], thyroid, and pancreas. The frequency of lymph node involvement is as follows: Peribronchial, retroperitoneal, cervical, mediastinal, mesenteric, portal, supraclavicular, and inguinal. Sometimes metastases are present only in one organ or organic system (brain, bone, heart, and adrenal).

The duration of the carcinomas of the lung varies with the malignancy of the tumor and the resistance of the patient. While most of the authors note a rather rapid course, Kirklin and Paterson state that their course is extraordi-

narily latent. Ewing quotes a duration from 10 days to four years, and Fishberg one of six months to four years. But these statements are of a dubious value because lung carcinomas cause late clinical manifestations, and sometimes none at all. On the other hand, there may occur occasionally an acute activation of a lung carcinoma after pneumonia.

Cancers of the lung may originate from the following three structures: a) the columnar epithelium of the bronchia and bronchioli, which may undergo (under pathalogical conditions) a metaplastic change into a squamous-cell type; b) the cuboidal epithelium of the peribronchial mucous glands; and, c) the flat polygonal cells lining the alveoli, which under pathologic conditions (atelectasis) may become cuboidal or low columnar in shape. The bronchiogenic carcinomas are the most frequent; cancers derived from the peribronchial glands occupy second place; and those originating from the alveolar cells are exceptional. Many investigators do not recognize the actual existence of the last variety, as it is still controversial as to whether the cells lining the alveolar spaces are histogenetically of epithelial or mesodermal derivation. Such theoretical considerations have little significance for several reasons. Pulmonary cancers have been reported closely imitating the alveolar structure of the lung in the presence of intact bronchiolar structures (Kretschmar; Gordon; Briese; Ribbert; Hueper; and Oberndorfer). Inasmuch as the mesodermal transitional epithelium, lining the dome of the urinary bladder, gives rise to malignant tumors morphologically identical with those originating from the entodermal epithelium, covering the trigonal and paratrigonal region, the histogenetically different, cellular elements composing the lining of passages whether they carry urine or air, seem to possess the same neoplastic potentialities.

The histological structure of pulmonary carcinomas depends upon the tissue of origin and the presence of metaplastic changes. There occur squamous-cell carcinomas with and without cornifications, round-cell carcinomas, adenocarcinomas of various degrees of differentiation and function (simple adenocarcinoma, papillary adenocarcinoma, and gelatinous adenocarcinoma), and highly anaplastic carcinomas of sarcomatoid appearance (the so-called oat-cell carcinomas). There has been in recent years a change in the numerical relation of the different histologic types, according to Probst, who claimed that a shift in favor of the cancroid variety of pulmonary cancer has taken place (squamous-cell type of cancer represents, according to various data, from 11.7 to 30.1 per cent of the total number). This investigator found in his series that from 1905 to 1912 there were 25 per cent cancroids, from 1919-1922 there were 38.5 per cent, and from 1923-1925 there were 42.9 per cent belonging to this type of carcinoma. Brandt reported that in his series there were 22.5 per cent squamous-cell carcinomas, 48 per cent basal-cell carcinomas, 9.5 per cent differentiated adenocarcinomas, and 20 per cent undifferentiated carcinomas. There were 17.2 per cent squamous-cell carcinomas in the series reported by

Brechwoldt; and Ewing recorded an incidence of 32 per cent of squamous-cell cancers, but rarely of the hornified type. In a more recent investigation of Olson comprising 69 cases, 42 per cent were of the squamous-cell type (28 per cent of them with cornifications), 24 per cent were adenocarcinomas, and 33 per cent were small-cell carcinomas.

5. THERAPY

The therapy of lung carcinomas is extremely unsatisfactory. The roentgen-ray treatment has a restricted value, because it impairs the tumor growth temporarily. Only the great minority of carcinomas of the lung can be operated on. The diffuse and bronchiogenic carcinomas of the vicinity of the hilum have to be excluded from surgical procedures. The well circumscribed, intralobular carcinomas offer the best chance for operation. According to Lenhartz, three different operations may be performed: 1. The tumor cavity may be opened after a thoracotomy, the disintegrated tissue removed and a thorough scraping of the wall done. Cures are not obtained with this method; 2. In carcinomas which have involved the chest wall, several ribs and a part of the lung are removed. Recurrences always follow this procedure; 3. The tumor is removed completely with sufficient surrounding healthy tissue. If necessary a whole lobe or whole lung may be extirpated. This method represents the only way to success. Sauerbruch; Lenhartz; Wolfsohn; Graham and Linger; and Overholt have used this technic, but rarely with good results.

6. CAUSATION OF INCREASED FREQUENCY

In view of the discouraging results of the therapeutic procedures, the prophylaxis of lung carcinomas becomes of utmost importance. Effective and intelligent preventive measures can be taken only if the cause or causes of the disease are known. Studies of the etiology of pulmonary cancers are of the greatest significance considering the growing incidence of this disease, which in some countries ranks second as a cause of cancer deaths in males.

The scientific interest in the etiological aspect of this increase has been remarkable. "No other form of neoplastic disease is more intriguing from the standpoint of incidence than primary carcinoma of the lung, for within a generation it appears to have become one of the common forms of malignant disease instead of the rarity which it was believed to be at the beginning of the century" (Weller). Numerous explanations have been suggested and many agents have been incriminated with more or less justification. The factors regarded as important in etiological respects may be divided into two main groups, according to their endogenous or exogenous character. In addition to these factors, which may account for an actual increase in the number of pulmonary cancers in late years, certain factors of statistical and technical nature which may have led to an apparent, but spurious increase of these neoplasms deserve consideration.

A. Factors of Technical and Statistical Nature

a. Improvement in Diagnosis

The claim has been advanced repeatedly that the increase in lung cancers is attributable to the marked improvements made in the diagnostic methods of lung diseases during recent decades (roentgen-examinations, especially with the help of intrabronchial lipiodol injections, stereoscopic pictures, and bronchoscopy). Doubtless such advancements, in conjunction with the establishments of specially equipped diagnostic departments and clinics for chest diseases in larger medical centers, and an increased general interest in pulmonary tumors among the medical profession, have resulted in the clinical discovery of a larger number of these neoplasms during the life time of the patients than in former years. The influence exerted by the existence of a bronchoscopic clinic upon the incidence of pulmonary tumors among the patient population of a hospital is strikingly illustrated by a report from the Jefferson Hospital, Philadelphia, Pa. The report was published by McCrae, Funk and Jackson, who recorded 53 cases of bronchial cancers in a total number of 621 necropsies. However, the clinical diagnosis of pulmonary cancer is often missed (Bahls). Wells reported only 10 per cent correct diagnoses, Fried 57 per cent, and Lubarsch and Seyfarth approximately 50 per cent. Statistical calculations, relying on clinical records or on death certificates based on clinical diagnoses, contain a wide range of error in the fundamental material, and are unreliable as to the absolute numerical conclusions reached.

It would be incorrect to consider any appreciable part of the recent increase in pulmonary malignancy as a spurious one because of the operation of this diagnostic factor. The incidence of these tumors has risen to a marked degree in the autopsy material of well-controlled institutions administered on scientific lines for many decades. While the introduction of a few minor improvements in the technical performance of autopsies and a more extensive use of histological examinations in recent years may have resulted in more reliable autopsy records, this scarcely can explain the marked increase of lung cancers observed. This is true particularly in view of the fact that the pathological description of this neoplasm has been a property of the pathologists since the days of Rokitansky; Virchow; Laennec; and Grawes. This rise cannot be attributed to any selection or change in selection of autopsies in most of the large hospitals, particularly those of the European continent, as these institutions do not use such a procedure. The percentage autopsies performed on patients dying in these hospitals has been uniformly high (80-90 per cent) for many years, and necropsies are practically routine measures. Clinicians do not exert any influence upon the type and number of necropsies performed in these institutions, which have been at all times under the direction of recognized authorities in the field of pathology. As the general type of patient entering these hospitals has not changed fundamentally in recent decades, the rise in

the incidence of pulmonary malignancy, as reflected in autopsy data, is not a spurious one. It represents an actual increase in so far as more persons have died in recent years from this blastoma than in the years before the turn of the century.

b. Change in the Ratio of Lung Cancers to All Cancers

It has been argued that the increased number of cures in certain types of cancers attained with modern therapeutic methods has brought about such a marked shift in the mortality rates of cancers of different organs that the pulmonary cancers with their infaust prognosis have received a larger share than in former years, thus producing the impression of an increased frequency. While it cannot be denied that curative results have been obtained during the last twenty years in a definitely higher percentage of cases of certain accessible tumors (breast, cervix, and skin), these therapeutic successes have not been sufficiently numerous to prevent a continuous considerable rise in the number of deaths from malignant disease occurring during the same period. The better therapeutic results obtained in a few types of tumors are too limited in number to have produced such a fundamental shift in the relative death rates from cancer of various organs that an apparent rise in pulmonary tumors would have resulted.

c. Overaging of Population and Its Effect Upon Statistical Data

Some investigators have advanced the conception that the appreciable lengthening of the human life span, which occurred during the past decades, may have brought about an increase in the number of pulmonary cancers observed, by enabling a larger group of persons to reach the so-called cancer-age. While such an explanation may account for a certain part of this rise, it would not provide a plausible reason for the extraordinary increase above that of other cancers. It is quite doubtful and uncertain whether the aging processes of the body play any important role in the causation of any malignant tumors. Observations from the study of occupational tumors indicate rather that the so-called cancer-age is mainly or entirely a coincidental phenomenon. For the average individual it runs parallel to the average exposure time essential for the production of a malignant growth under average conditions.

It appears not only quite possible but entirely probable that the increased longevity has provided an opportunity for a larger group of persons to receive an exposure of sufficient duration to some carcinogenic agent, and thus to respond with a pulmonary cancer. At the same time, a possible increase in the number of extraneous carcinogenic agents, occurring in recent decades, may have brought a larger proportion of the general population into effective contact with these factors, producing an actual increase of pulmonary cancer during the "cancer-age," but unrelated to it. Observations made with occu-

pational cancers of the lung in man and with spontaneous and experimental pulmonary tumors of mice suggest that the advent of new and powerful exogenous carcinogenic agents at the end of the last century might be presupposed, if the increase in the frequency of pulmonary malignancy would have been accompanied by a shift of the manifestation time into younger age groups. On this point the following information is available in the literature.

In a series of 44 cases observed by Ask-Upmark, between 1890 and 1930, the age range for men with lung cancer was 30-76 years (average 51 years) and for women 43 to 66 years (average 56.5 years). In the series of 60 carcinomas seen between 1923 and 1933, of which 74.5 per cent occurred in males, Haintz reported an age range of 36 to 70 years (average 56 years). A more detailed analysis of the age distribution of their 202 cases, observed between 1922 and 1926, was given by McCrae, Funk and Jackson. Their data are presented in the following table:

Years	*16-30*	*31-40*	*41-50*	*51-60*	*61-70*	*70 and more*
Cases	6	29	49	65	34	6
Percentage	3	15	26	35	18	3

In connection with his survey of lung cancer among the American veterans, Matz published the table on page 386 compiled from the data of 8 investigators reporting 1,814 cases.

The age correlation in Matz's own series of 138 cases, occurring between 1927 and 1937 in American war veterans, showed a definite shift toward younger age groups. He attributed this fact to the younger average age of the veterans compared with that of the civilian population. He anticipated an increasing incidence of pulmonary malignancy among the veterans in the coming years as they approach the higher age groups.

Age Incidence of Bronchiogenic Carcinoma-Matz

Years	*20-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70 and over*
Percentage	1.4	25.4	48.6	18.8	5.1	0.7

The data, contained in the collective statistics of Matz, are in general agreement with those obtained by Simons on an even larger series of cases (2,786). Simons observed that 22.4 per cent of them were found in the age group 41-50 years, 34 per cent in the age group 51-60 years, and 24 per cent in the age group 61-70 years. In all, 80 per cent occurred in persons between 40 to 70 years old, and only 14 out of 5,217 cases were younger than 20 years.

The data available do not supply any reliable and comprehensive information from which a chronological analysis of the age distribution of lung cancer, during the last five decades, can be made. No conclusion can be drawn regarding the question as to whether or not pulmonary cancer in recent years became manifest more often at an earlier age than in former times.

AGE INCIDENCE OF BRONCHIOGENIC CARCINOMA
(MATZ)

Age Group, Years	Rogers		Hill		Olson		Arkin and Wagner		Harvey		Frissell and Knox		Simpson		Brines and Kenning		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Unrecorded	—	—	22	2.2	—	—	—	—	—	—	—	—	—	—	—	—	22	1.2
10–20	—	—	—	—	—	—	—	—	—	—	1	2.2	4	2.9	—	—	5	0.3
20–29	—	—	65	6.6	12	4.1	3	2.2	4	4.0	3	6.5	6	4.3	1	1.5	94	5.2
30–39	2	4.0	139	14.2	25	8.5	9	6.7	14	14.0	5	10.9	18	12.9	10	14.7	222	12.2
40–49	7	14.0	257	26.2	53	17.9	39	28.9	23	23.0	6	13.0	41	29.5	18	26.5	444	24.5
50–59	24	48.0	300	30.6	105	35.6	59	43.7	32	32.0	17	37.0	45	32.4	27	39.7	609	33.6
60–69	12	24.0	198	20.2	60	20.3	22	16.3	19	19.0	14	30.4	21	15.1	10	14.7	356	19.6
70–79	5	10.0	—	—	30	10.2	3	2.2	8	8.0	—	—	4	2.9	2	2.9	52	2.8
80 and over	—	—	—	—	10	3.4	—	—	—	—	—	—	—	—	—	—	10	0.6
Total	50		981		295		135		100		46		139		68		1.814	
Average	50.7		51.0		53.7		—		—		—		4.8					
Youngest	37		—		29		—		21		17		13					
Oldest	77		—		89		—		—		69		77					

B. Endogenous Factors

a. Heredity and Congenital Predisposition

The importance of endogenous factors in the development of lung cancers and their significance in connection with the recent increase of these tumors has remained an unsettled question. Among the endogenous factors of pulmonary nature, which may predispose to tumor development in the lung, some are of a local type, such as malformations, epithelial displacements, fetal atelectases and cyst formations, and bronchial papilloma. Others are of a diffuse type, representing a congenital or inherited susceptibility of the lung tissue to neoplasia in response to some additional endogenous or exogenous stimuli. Local predisposing factors (Cohnheim's theory) do not play any important role in the great majority of lung tumors, and the recent rise in the frequency of these neoplasms provides additional evidence to this effect, and minimizes their significance (Lorentz).

On the other hand, it is uncertain if hereditary influences are active to any appreciable degree in the causation of pulmonary neoplasms in man. While great importance is attached to a hereditary factor by Fischer-Wasels as well as Macklin in this respect, the supporting evidence for such an assumption is missing. Suggestive evidence for the existence of a hereditary factor is deduced by Matz, based on the fact that a family history of cancer could be elicited in 15.2 per cent of his cases. This figure is considered by him as the lower limit, as many histories of his series did not mention an inquiry as to the occurrence of cancer among the members of the family. Similarly, Simons reported the presence of a hereditary factor, as 64 out of 930 cases of lung tumor showed a family history of cancer. Such a reasoning appears far-fetched, considering the fact that approximately 10 per cent of all adults die from cancer of some kind. It does not seem likely that an endogenous factor of a hereditary nature has assumed any important and leading part in the development of the pulmonary cancer trend exhibited during recent decades, especially as this movement is generalized. It is out of the question that the genetic qualities of the population of many peoples in several continents should have suddenly undergone uniform fundamental biological changes resulting in a higher inherited susceptibility to pulmonary neoplasia. A hereditary intrinsic factor may have participated in this phenomenon in a passive way; that is, an increase in the number and intensity of external carcinogenic agents may have activated the inherited factor, and thus supported the development of lung cancer at some later period of life (Weller). The possibility of such an interrelation is suggested by observations made in mice (Slye; Andervont; Lynch; and Bittner).

There exists sufficient and reliable evidence attesting to the importance of hereditary factors in the development and incidence of pulmonary adenomas and carcinomas in mice. It has been shown definitely that the relative

frequency of pulmonary neoplasms in different strains of mice is dependent upon genetic factors peculiar to the individual strains. These pulmonary tumors become manifest usually at an advanced age. They do not appear before the eighth month of life (Lynch), and rarely before the thirteenth month; but are found most frequently during the latter half of the second year (when mice approach senility), and reach their peak after the passing of this period. The development of a lung tumor in the individual mouse with a suitable genetic susceptibility depends upon the fact that this inherited factor is activated by some requisite environmental intrinsic or extrinsic agent. In the absence of such a stimulus a mouse with an inherited susceptibility to pulmonary neoplasia may grow old without ever developing a lung tumor (Lynch). This important and apparently essential correlation between the hereditary factor and the activating, environmental extraneous agent is demonstrated strikingly by experiments in which chemicals (tar, 1.2.5.6-dibenzanthracene, and methylcholanthrene) with known carcinogenic properties provided the additional activating stimulus (Andervont; and Lynch).

Repeated applications of tar to the skin of mice, alternating the site of application to impair the chances of the production of cutaneous tumors, resulted in an increase of the incidence of pulmonary tumors in strains of mice with a genetically known susceptibility to "spontaneous" pulmonary neoplasms (Lynch) (strain I: spontaneous incidence 37.04 per cent, in tarred series 85 per cent; and strain II: spontaneous incidence 6.75 per cent, in tarred series 22 per cent). Similar effects were produced in mice by the injection of 1.2.5.6-dibenzanthracene and methylcholanthrene, respectively (Lynch; and Andervont) (the incidence was increased in one strain from 31.8 per cent normally to 81.4 and 89.9 per cent, respectively, after injections with dibenzanthracene). The absolute results obtained depended upon the genetic constitution of the particular strain used and on the dose, interval, and duration of treatment with the given carcinogenic substance.

Regardless of the genetic differences in the various strains used, the action of the carcinogenic agent upon the incidence of pulmonary tumors was always demonstrable when large amounts of these chemicals were applied (Andervont). With massive doses it was possible to wipe out any strain differences of resistance, and to bring out any symptomatically silent inherited susceptibility. These conclusions were drawn by Andervont from observations made on eight strains, some of which did not show any spontaneous lung tumors normally. The degree of inherited susceptibility and the effect produced by the administration of carcinogenic agents was calculated from the percentage of mice developing tumors, the number of neoplasms in the individual mouse, and the length of latency period. In addition to effecting an increase of lung tumors among the whole group of treated mice, there occurred, under the influence of these chemicals, a rise in the number of pulmonary tumors in the

individual animal (Andervont; and Lynch). It was noted by Lynch that mice painted with tar developed lung tumors at an earlier age than normally, confirming observations previously made by Murphy and Sturm.

The exact way through which these chemicals and tar act upon the lung tissue is still uncertain. It may be possible that the tar after penetration into the skin, and the subcutaneously injected dibenzanthracene and methylcholanthrene may enter the blood or lymph and thus reach the lung. The tar may be inhaled in the form of dust after drying and get into the lungs, or it may be licked off and enter the body through the alimentary tract. This substance may exert a specific, local, pulmonary influence or a general carcinogenesis favoring one. While Cook and his co-workers contended that these extraneous agents summate with the naturally occurring carcinogenic factor to give an effective stimulus, Andervont came to the conclusion that the appearance of lung tumors in strains which normally do not show spontaneous pulmonary neoplasms indicates that heredity is not an essential requisite for the production of these primary blastomatous responses in the lung. The existing variations in susceptibility are not of a fundamental nature, in the opinion of Andervont, but merely matters of degree. This investigator succeeded in producing in a strain of mice, showing a high incidence of spontaneous pulmonary malignancy, pulmonary tumors in practically 100 per cent, after the subcutaneous administration of sufficiently high doses of 1.2.5.6-dibenzanthracene. He was, also, able to induce the development of such neoplasms in several strains of mice, refractory to spontaneous pulmonary neoplasia.

b. Sex

The incidence of lung cancer is much higher in males than in females. In different statistical studies the ratio varies through wide ranges, according to Simons (males 59-91 per cent, females 9 to 40 per cent); Haintz (74.5 per cent males); Hill (77.9 per cent males); and Kraft (89 per cent males). In the survey made by Simons, there was an incidence of 80 per cent in males in the 5,121 compiled cases of lung cancer. The recent increase in lung cancer, according to this investigator, did not affect the sexes in all districts in the same way; there was a greater incidence among men than among women (Peters; and Kennaway and Kennaway). In more recent years the increase rate in both sexes has become practically equal. Similar sex relations exist regarding the incidence of laryngeal cancer. The sex distribution of laryngeal cancer is, according to Kraft, 20 men to 1 woman. The reason behind this divergent behaviour of the sexes is not known definitely. From experimental evidence Lynch as well as Campbell have concluded that sex as such has little or no effect upon the incidence of spontaneous and experimental pulmonary tumors in mice.

Andervont asserted that 1.2.5.6-dibenzanthracene brings about neoplastic response in the lung more rapidly in male than in female mice. He observed

further that the same type of reactivity persisted through two generations injected with this chemical. From the evidence presented and discussed it appears extremely unlikely that sex plays any important role in controlling the neoplastic reactivity of the lung tissue in human beings. Extraneous environmental factors including those of occupational nature seem to determine the preponderance of pulmonary and laryngeal blastomas in males (Adler). There was no evidence supporting the existence of racial relations in connection with lung cancer in the series of these tumors studied by Jaffé.

C. Exogenous Factors

"In looking for the cause of the increase in pulmonary malignancy one should look for a change in environmental conditions which took place toward the end of the last century" (Boycott). This conception is evidently in harmony with that held by numerous investigators, who have attempted in recent years to find an explanation for this alarming development. The various extrinsic factors which have been incriminated in this respect may be divided into bacteriotoxic, chemical, and physical agents of nonspecific or specific nature.

a. Bacteriotoxic Agents

1. Tuberculous infection and chronic pulmonary lesions, especially cavities and bronchiectases, frequently associated with this disease, have been regarded by Ewing; Kraft; Fried; and Derischanoff as one of the more significant causes of pulmonary cancer. Ewing has claimed that pulmonary tuberculosis represents the main source of cancer of the lung. A similar view was expressed by Kraft, who found pulmonary tuberculosis present in 46.7 per cent of his 150 cases of primary carcinoma of the lung. Derischanoff recorded the coexistence of cancer and tuberculosis in 16.7 per cent. The investigations of numerous other workers do not support such a contention (Wahl: 9.8 per cent cancer of lung associated with pulmonary tuberculosis; Kikuth: 8.7 per cent; Seyfarth: 2 per cent; Brechwoldt: 8.5 per cent; Olson: active Tb. in 1.6 per cent, healed Tb. in 5.9 per cent, total 7.4 per cent; Probst: 5 per cent; and Matz: 2.1 per cent). The existence of important causative relationships between pulmonary tuberculosis and cancer are not recognized by Simons; Hochstetter; and Ferenszy and Matolscy. While Olson pointed out that the incidence of tuberculosis in cancer of the lung is roughly in accord with the known incidence of tuberculosis in unselected cases, Geigel asserted that pulmonary tuberculosis represents a condition which exerts a certain antagonistic effect against the development of carcinoma of the lung. A bronchiogenic carcinoma originates occasionally from the metaplastic epithelium of a tuberculous bronchiectasis. On the other hand, tuberculous infection of the lung has no causative relation to the majority of pulmonary malignancies, and does not play any role in the production of the recently observed increase of this tumor variety. Such an interrelation is less plau-

sible as the great improvements made in recent years, in the prevention and therapeutic control of tuberculosis, have resulted in a remarkable reduction of the mortality from this infection, and in a diminution of the number of the more severe tuberculous lesions in the lung, including cavity formation.

2. Syphilitic bronchial scars and other nonspecific bronchiectatic formations have furnished allegedly, in a few instances, the soil in which pulmonary cancers developed.

3. Late bronchial changes, following an influenza infection and characterized by atypical, metaplastic, epithelial proliferations of the bronchial mucosa, have supplied the basis for the contention that the recent increase in pulmonary neoplasms is related etiologically to the influenza epidemic which ravaged the world in the years 1918 to 1919 (Askanazy; Schmidtmann; Winternitz; Berblinger; Mayer; Peek; and Probst). Winternitz went so far as to predict in 1920 the rise of lung cancers in the years following, because of these bronchial lesions which he observed as frequent sequelae of influenza. This assumption was not confirmed by other investigators from an analysis of the precancer history of their cases (Gottstein; Seyfarth; Staehelin; Kikuth; Mönckeberg; Brechwoldt; Hanf; and Syrek). Hueper pointed out that a similar increase of lung cancer did not follow the great influenza epidemic of 1888-1889, and that the beginning of the present increase started many years before the influenza epidemic of 1918-1919. The actual existence of such an interrelation becomes still less probable in view of an observation made by Kerlev (cited by Matz). He found that the inhabitants of Iceland are free of lung cancer in spite of the fact that the influenza epidemic was exceptionally severe on this island.

An evaluation of the evidence available on the causative significance of bacteriotoxic agents regarding pulmonary malignancy permits the following conclusion. These agents or the conditions set up by them in the lung may have been responsible for, or may have contributed to, the development of some isolated cases of lung cancer. The majority of these tumors have no connection with them, and the recent increase in pulmonary neoplasms is entirely unrelated to them.

b. Chemical Agents

Numerous chemical substances of well or ill defined chemical nature and of occupational or non-occupational character have been incriminated in causing, contributing to, or precipitating the development of pulmonary malignancy, and in having some share in the recent rise of these neoplasms. The great number of substances, their marked diversity in character, and the many contradictory opinions expressed as to their causative significance reflect the high degree of uncertainty existing in regard to the potential carcinogenic action of many of these agents. Some investigators stated that the analysis of their case histories did not furnish any evidence supporting the conception,

that certain general environmental factors or some occupational hazards of chemical or physico-chemical character played a significant role in the production and increased frequency of pulmonary tumors (Haintz; Rice; Koelsch; Bonser; Fischer-Wasels; and Shennan). Other workers suspected or directly blamed one or several extraneous agents as being prominently involved in this respect.

I. ILL-DEFINED OCCUPATIONAL AND NON-OCCUPATIONAL CHEMICAL AGENTS

Prolonged environmental and occupational exposure to dust without regard to its chemical nature, but with emphasis on the quantity inhaled, is considered by many as a cause of the chronic inflammatory conditions of the bronchial and pulmonary epithelium, which may lead to cancerous processes of these tissues. The chronic bronchitis, chronic interstitial pneumonia, and fibrosis (pneumoconiosis) set up in the lung, by the inhalation and deposition of dust particles, give rise to the development of regenerative, metaplastic, epithelial proliferations; or they may activate preformed metaplastic lesions (post-influenza) and prepare the soil for a subsequent malignant transformation of these epithelial changes (Ssipowsky; Tuttle and Womack; Katz; and Hampeln). In the opinion of Hampeln, bronchiogenic carcinoma is a dust inhalation disease. An augmented production of dust, resulting from the rapid expansion of industrial activities and the marked rise of vehicular traffic during recent years (affecting, especially, the thickly populated industrial districts and big cities), is implicated in the increase of pulmonary malignancy among the general population during the same period, according to Dissmann; Schmidt; Ewing; Brandt; Ferenszy and Matolscy; Maternia; Heilmann; Ménétrier; Ribbert; Moise; Rostoski; Rostoski, Saupe and Schmorl. This conception was supported by the observation that lung cancer is found more often in domesticated animals exposed extensively to the inhalation of street dust (horses, cattle, sheep, and dogs) than in those living in rural areas (Joannovič; and Sticker); while wild animals were supposed to suffer only from benign pulmonary adenomas (Fox).

A similar reasoning has been applied by many workers to connect the genesis of lung cancers and their recent rise in incidence with the more generalized occupational exposure to industrial dust. A relatively higher frequency of pulmonary malignancy among persons exposed occupationally to the inhalation of solid particles (street dust, stone dust, metal dust, coal dust, and glass dust) was recorded by Seyfarth. The late increase of pulmonary malignancy among inhabitants of the Dresden district was related by Schmorl to the production of chalicosis among workers of the sandstone industry, and of anthracosis among coal miners there. Workers employed in the following dusty industries: manufacture of pottery, metallurgy, building trades, and tobacco plants, have an increased liability to lung cancer, according to Simpson. Harvey reported from Australia that 38 per cent of the cases with

lung cancer had been exposed to noxious types of dust during their work (quartz, gold ores, copper ores, tin ores, and coal). The greatest susceptibility to lung cancer was displayed by workers exposed to house dust. Among men engaged in dusty occupations, an especially high incidence of lung cancer exists in grooms (Hudson). In the series reported by Duguid, there were 72 outdoor workers against 71 indoor workers. Since three-fourths of the population is represented by indoor workers, the incidence of lung cancer is three times higher in outdoor workers than in indoor ones, who are exposed to the inhalation of dust to a lesser degree than the former, in the opinion of Duguid. This investigator believed that this evidence supports the causative significance of dust in the development of pulmonary malignancy. Schachter emphasized the etiological importance of a dusty occupation for the production of lung cancer. Among 898 cases of lung cancer, collected by Brochbank, 61 cases had occupational exposure to some kind of dust (18 metal workers, 15 cigar makers, and 28 carpenters); while in Brockbank's own series of 62 cases, 9 or 14.5 per cent were associated intimately with dust and 18 or 29 per cent were exposed to fumes. Among the cases, reported by Ferenszy and Matolscy, 43 per cent came from professions with a dust or fume hazard. Occupational exposure to tobacco dust has figured prominently in the studies of several investigators concerning a carcinogenic dust hazard. Rottman listed cigar makers, metal workers, and spinners among professions most often affected by pulmonary malignancy. Similar claims have been made by Wacker and Schmincke; Krompecher; Langbein; Behla; Heilmann; Benda; Borst; Ferenszy and Matolscy; Enger; Brinkmann; and Seyfarth. Cigar makers, sorters, dealers, and other tobacco workers have been cited as showing an increased liability in this respect and Jaeger and Kolbe considered cancer of the lung as an occupational disease of tobacconists. Cancer of the respiratory tract was found to be especially frequent among male workers of certain Sheffield trades connected with metallurgic industries (machinists, foundry workers, and metal grinders) (Turner and Grace). An occupational exposure to dust was present in 20 per cent of the cases reported by Ask-Upmark, and in 75.4 per cent of those recorded by Rosedale and McKay. From death certificates of England and Wales for the years 1920 to 1932, Kennaway and Kennaway obtained the following correlations between dusty occupations and incidence of lung and larynx cancer. A rather high excess of these neoplasms was statistically found in workers exposed to road dust [paviours, street cleaners, dustmen, and drivers of horse drawn vehicles and automobiles (chauffeurs had a normal rate of larynx cancers)], masons, concretors, council workers, workers exposed to producer coal gas and tar products, pottery makers, French polishers, tobacconists, and metal grinders (silica exposure); while a low lung cancer death rate was found among workers of the agricultural and mining industries, and cotton mule spinners (crude oil exposure), a normal liability existed among carpenters and grooms of horses. As no special occupation

seemed to account for the total increase of lung cancers, Kennaway and Kennaway concluded that industrial hazards did not play any important role in this connection.

A similar opinion was expressed by Harris, who observed in a series of 117 cases of laryngeal carcinoma (age, 39 to 53 years), 6 cases of laryngeal cancer and two lung cancers in coal miners after an occupational exposure to coal dust for 15 years or longer. The actual incidence of laryngeal cancer is not as high in miners as in occupational groups not exposed to a dust hazard. Occupational exposure to wood dust was blamed by Sekoulitsch for the increased occurrence of cancer of the larynx, tonsil, and base of the tongue in carpenters and cabinet makers. Benign laryngeal tumors have been related etiologically to an excessive, occupational, mechanical stress of this organ, such as existing in singers, teachers, officers, and professional speakers (Kahler); consequently, significant excess of laryngeal cancer exists among musicians and a doubtful one among teachers (Young and Russell).

The negative attitude of Kennaway and Kennaway toward the causative role of dust in connection with pulmonary malignancy is shared by Fischer-Wasels; and Landis. The fundamental contention that there has been an increase in street dust in late years was challenged by Teleky, who pointed out that in spite of greatly increased traffic, the production of dust had decreased in comparison to former years because of better road conditions. Street dust does not possess any carcinogenic significance in the opinion of Berblinger; Kikuth; and Schmidtmann. The absence of an excessive incidence of lung cancer among persons especially exposed to street dust (policemen, trolleymen, teamsters, chauffeurs, street workers, and street venders) was cited by Probst in refutation of the theory of a carcinogenic action of this substance. A similar conclusion was reached by Pancoast and Pendergrass, who observed three cases in which a lung cancer occurred in association with pneumoconiosis. These investigators felt that the report of isolated cases of bronchiogenic cancer among coal miners, stone cutters, cigar makers, and men engaged in many other dusty occupations did not render conclusive evidence to warrant any definite decision. A concurring opinion on this subject was expressed by Saupe, who added that the physical examinations, conducted by Krüger, and Rostoski and Thiele, on workers of various dusty industries (stone masons, workers in pottery factories, cigarette plants, bronze works, and asbestos plants, and bakers) did not yield any evidence of a causal relationship between pneumoconiosis and pulmonary carcinoma. Observations made by Feil in France caused him to state that lung cancer is not frequent in workers exposed to dust (coal and iron miners).

The etiological significance of tobacco dust was questioned by Lehmann, who pointed out that persons engaged in the tobacco trade are, in general, heavy smokers, and that this habit is more likely to be of causative importance than the exposure to the tobacco dust. The presence of pneumoconiosis in

only 2.9 per cent of Olson's series of pulmonary malignancy does not support the conception of a significant causative role of dust in the genesis of this type of neoplasia. It was pointed out by Duguid that the smoke abatement campaign, which was conducted in England some time ago and which resulted in a considerable decrease of the solid particles in the air, was not followed by a decrease in the incidence of lung cancer. The dust theory of lung cancer does not explain, in the opinion of Assmann, the marked regional differences in the incidence of lung cancer existing among certain industrialized districts in Germany (Saxony: high lung cancer rate; Ruhr district: low lung cancer rate). The evidence favouring the dust factor is not too convincing in the opinion of Stout, who refers to a statement of Huguenin. This author remarked that there was no increased incidence of lung cancer among miners of England, France, Germany, and Belgium.

From an evaluation of these contradictory data it is quite apparent that dust as such, irrespective of its chemical character, is not conducive to lung cancer (Kennaway; Kikuth; and Assmann). The evidence cited presents, perhaps, the most striking illustration of an error repeatedly committed in connection with statistical investigations on the cause of environmental and occupational tumors. It must be considered a fundamental fallacy, if an attempt is made to find the extraneous carcinogenic agent of a certain neoplasm by determining statistically its incidence among members of large occupational groups (chemical workers, miners, and metallurgical workers), comprising an indefinite and multifarious conglomeration of smaller and larger groups of workers exposed to environmental influences of the most diversified nature. Even in smaller occupational groups a certain hazard may vary greatly in intensity and duration, and in effect, as far as the various members are concerned and depends upon the type of work in which they are engaged. Therefore, it becomes clear beyond any doubt, that no reliable or conclusive information can be obtained when large occupational groups are evaluated. This consideration applies to an even greater degree when general classes of individuals, such as outdoor and indoor workers, are analyzed. The result of such an approach usually causes not a clarification but an increased confusion of an already complex situation. The concept of the "chronic irritation" theory of carcinogenesis, still considered by many workers as a plausible explanation of this biological phenomenon, has furnished the "scientific" basis for such a mistaken and futile approach.

The recent developments of experimental and occupational cancer research have demonstrated rather definitely that chemically specific agents rather than non-specific irritative factors, such as dust in general, play an important and essential role in the production of malignant neoplasms. Moreover an outstanding histologic feature of the development of experimentally induced pulmonary tumors in mice was the absence of any inflammatory changes in the precancerous and early cancerous lesions (Andervont). The investigations deal-

ing with the potential carcinogenic action of certain well-defined, abnormal, atmospheric ingredients are of greater scientific significance and have produced more reliable and definite information.

II. CHEMICAL AGENTS OF DEFINED TYPE

The exposure to the inhalation of chemically well-defined substances is to a large extent restricted to industrial hazards. The industrial exposures consist of contact of the respiratory organs with abnormal atmospheric ingredients present in the form of dust, fumes, vapors, and gases of the most varied types. Non-occupational contact with atmospheric contaminants is limited to the inhalation of coal dust, soot, carbon monoxide, sulfur dioxide, and, in some mining regions, arsenicals [smelting of arsenic containing ores (copper, iron, and silver)].

Silicosis

Silicosis, which is second only to anthracosis the most frequent type of industrial pneumoconiosis, has been incriminated by Fine and Jaso; Dible; and Charr as direct or indirect cause of pulmonary cancer. There are approximately 40 to 50 verified cases on record in which these two pulmonary conditions coexisted (Dible; Fine and Jaso; Klotz and Simpson; Klotz; Maxwell; Sladden; Middleton; Sweany; Porsche and Douglass; Vorwald and Karr; Allen; Sokoloff; Pancoast and Pendergrass; Simons; Schnurer; and Charr), when combinations of asbestosis and lung cancer are excluded from this list. Silica belongs to the biologically active types of dust (in contrast to the inert types, such as carbon), which are capable of exciting a characteristic tissue response of fibrotic nature in the lung (Gardner) by causing foci of chronic inflammatory irritation. Silicotic pneumoconiosis fulfills all the requirements which may be asked from a nonspecific carcinogenic agent acting on the basis of the chronic irritation theory of carcinogenesis.

A recent analysis of the pulmonary cancer incidence in 50 cases of silicosis observed from 1925 to 1936 by Klotz led this author to believe, that the liability to pulmonary malignancy was excessive in silicotics compared with that of the general population. There were four cases of lung cancer in this group, whereas 53 lung tumors were found among 4,500 necropsies performed during the same period. Only one of the silicotic cases with lung cancer was employed as a miner, while the others belonged to different occupational groups, such as metal workers, laborers, and gas company employees. A marked pulmonary fibrosis was present in only one case; this condition was of minimal or slight degree in the rest of the cases. The type of evidence, advanced in support of the conclusion drawn, cannot be admitted as adequate. In view of the great practical and scientific importance of this potential interrelation, it is fortunate that a number of very comprehensive, reliable, and thorough clinico-statistical studies have been made and have led to a definite decision concerning this question.

Important autopsy observations made on South African gold miners, in whom silicosis is of frequent occurrence, were used in a study of the alleged causative interrelation of lung cancer in silicotic individuals (Reports of the Miner's Phthisis Medical Bureau of South Africa, 1932 and 1935). Among 3,215 autopsies performed on European males employed in the mines or members of the white population of Johannesburg (deaths in the Johannesburg General Hospital), there were 16 cases of lung cancer during a period of eight and a half and eleven years, respectively (report of 1932). The relative percentage of lung cancer of these groups was as follows:

	European Non-Miners	*Miners without Silicosis*	*Miners with Silicosis*
Autopsies	1023	1109	1083
Per cent of Lung Cancer	0.58	0.54	0.37

Similar relations were stated in the report of the year 1935

Autopsies	1393	1679	1438
Lung cancers	13	12	10
Per cent	0.93	0.71	0.70

These data, obtained through post-mortem examinations, indicate clearly that the presence of a silicosis does not predispose or favor the development of a pulmonary malignancy. Similar extensive studies of the question, based on the roentgenological and clinical examinations of persons exposed to dust, were reported by Vorwald and Karr, using evidence collected from the literature and their own observations. The following tables are taken from the paper of these two investigators:

Incidence of Pulmonary Tumors in Clinical and Roentgenological Examinations of Individuals Exposed to Dust, as Reported in the Literature

Number of Cases	*Non-Silicotics*	*Silicotics*	*Pulmonary Tumor*
57,362	45,156	12,206	3(0.005%)

Incidence of Pulmonary Tumors as Revealed by Serial Chest Roentgenograms in Individuals Exposed to Dust and Examined in the Saranac Laboratory

Occupation	*Number Examined*	*Pulmonary Tumor*
Iron Mines	7,324	3
Foundries	6,613	0
Cement plants	823	0
Gypsum plants and mills	762	0
Copper mines	65	0
Silicotics	1,357	1 (0.074%)
Non-Silicotics	14,230	2 (0.014%)
Total	15,587	3 (0.019%)

Incidence of Carcinoma Seen at Autopsy in Individuals Exposed to Dust and Examined in the Saranac Laboratory

Number Examined	*Years Exposed*	*Silicotics*	*Carcinoma*	
			Pulmonary	*Non-Pulmonary*
178	1-46	136	2 (1.12%)	4

"In the remaining 176 cases without pulmonary carcinoma, proliferation of the respiratory epithelial elements was not observed. This obtained even though pulmonary dust fibrosis was often massive and had compressed many epithelial-lined air passages" (Vorwald and Karr).

The conclusion reached by these two investigators is that the inhalation of silica dust cannot be considered as an etiological factor in the development of primary pulmonary carcinoma.

This decision is corroborated by studies, conducted by Schulte and Schulz, on miners employed in the Ruhr district, where silicosis is frequently observed. Schulte even expressed the opinion that silicotic lungs provide a poor soil for the growth of a malignant tumor. Allen, who agreed with this opinion, stated, in connection with a report of two cases of anthracosilicosis associated with pulmonary carcinoma in coal miners of Pennsylvania, that pulmonary carcinoma was rare among coal miners of that part of the country, according to evidence supplied by roentgenological examinations.

There do not exist any experimental observations which support the existence of causal interrelation between the inhalation of silica dust and lung cancer. Guinea pigs, exposed to the inhalation of dust containing 98 per cent silicon carbide three to four days a week, 50 hours per month for 18 to 31 months, did not develop any pulmonary cancers (Willis; and Willis and Brutsaert); but seven animals showed adenomatoid formations in the lung at autopsy. Since similar lesions occur spontaneously in the lungs of guinea pigs (Sternberg; and Leitch) without leading to malignancy, the interpretation of these nodes under experimental conditions remains doubtful. Similarly negative results were obtained by Vorwald and Karr in a series of 3,338 animals of various species (guinea pigs, rabbits, rats, mice, cats, and chickens) exposed to the inhalation of varying types of dust for periods extending up to 749 days. The majority of substances used in these experiments were silicates (chalcedony, quartz, granite, chert, asbestos, and carborundum). The table appearing on page 399 prepared by Vorwald and Karr summarizes these studies.

Clinical as well as experimental evidence indicates that the common types of silica dusts do not possess any direct or indirect carcinogenic properties in connection with the development of pulmonary malignancy. This statement may not apply in regard to the inhalation of the special types of silicates contained in asbestos. Clinical observations, made during recent years, arouse the suspicion that the occupational inhalation of asbestos dust has a certain causal relationship to the production of bronchiogenic carcinomas.

Type of Dust	Guinea Pigs	Rabbits	Rats	Chickens	Mice	Cats	Pulmonary Tumors
Chalcedony	242	28			40		0
Quartz	894	41	201	12	24	4	0
Marble and quartz	25						0
Hematite and quartz	28						0
Quartz and gypsum	88		27		6		0
Granite	298						0
Chert	196	3	52		10		1
Hematite	106		31				0
Asbestos	235						0
Soft coal	37						1
Fluorspar-crude			15				0
Carborundum	213						0
Marble	172		12				0
Gypsum	200		12				0
Total	2832	72	338 3338	12	80	4	2 0.06%

Asbestosis

Chemical and Technological Aspects. Asbestos, designating a group of silicate minerals of crystalline fibrillar structure, was known to the ancient world. At that time and during the following centuries it was used occasionally in the production of perpetual lamp wicks, shrouds for cremation, and other purposes partly of curiosity character. It was only since the latter third of the last century that this material has attained a major industrial importance, and has become of serious significance from the standpoint of industrial hygiene.

Asbestos is distributed widely in the world but occurs in relatively few places in sufficient quality and quantity to make mining profitable. The chemical nature of commercial asbestos varies with the site of its occurrence.

1. Amphiboles, found in Italy, South Africa, and Australia, occurs in five varieties: a) tremolite is a white, brittle, calcium-magnesium silicate; b) actinolite is a mineral consisting of fibrillar or radiating crystals; c) hornblende-asbestos or amphibole-asbestos is a flexible, greenish, fibrillar matter containing much calcium and a high amount of silicic acid; d) mountain leather, mountain cork, or mountain wood is of a greyish or brownish color occurring in the form of sheets of interlacing fibrils; e) crocidolite, which is mined mainly in Australia and South Africa, has a bluish color, a silky lustre, and elastic fibers of considerable length and tensile strength, and is a soda-iron silicate. These types are usually very acid resistant, but less fire resistant.

2. Serpentine and its subvarieties, picrolite and chrysolite, are hydrated magnesium silicates in which the magnesium may be replaced by iron in

some types. The serpentine has a bandy or slate texture and may contain traces of nickel and copper. It is mined in Canada, Russia (Ural Mountains), Germany, Corsica, France (Pyrenees), Siberia, and South Africa.

The Canadian asbestos, mined at Thetford near Quebec, where approximately 78 per cent of the world production is obtained, consists of 33 parts of magnesium, 41 parts of silicic acid, and 5.75 parts of iron oxide (Oliver); while South African asbestos is composed of 2 parts of magnesium, 50 parts of silicic acid, and 40 parts of iron oxide. Italian asbestos contains 42 parts of silicic acid, 38 parts of magnesium, and 3 parts of iron oxide. None of the various types possesses any free silicic acid.

The production of asbestos has risen enormously in recent years. It received this great impetus from its use in the automobile industry. The total production in 1868 was two hundred tons; in 1880, five hundred tons; in 1925, 330,000 tons; and in 1929, 430,000 tons. The United States is the principal consumer of this product. More than 12,000 persons are employed in the chief asbestos plants of this country. Occupational contact with asbestos is present in many industries using asbestos products. Asbestos is employed for a great variety of purposes, such as the manufacture of incombustible and insulating materials (fire resistant clothes, blankets, theater curtains, sheets, ropes, cords, twine, and threads), filter cloths, mill-board, wall board, shingles, tiles, mortar (together with cement and plaster of Paris for providing a fireproof wall lining), clinkers, gaskets, packing material of pumps, insulating material of steam pipes, water pipes, boilers, and electric wires, brake lining, paper, mattresses, adsorbent of dyes (for manufacture of fire proof and acid proof stains), ingredient of rubber products, and artificial wood (mixed with wood powder) (Lanza; Lynch; Stewart, Bucher and Coleman; Ullmann; Encyclopedia Britannica; Dewirtz; Nordmann; Alwens; and Cooke). The fibrillar types are spun, twined, and woven, while the brittle varieties and the dusty waste are compressed and molded into the desired shapes.

Conditions and Types of Exposure. The chief health hazard consists in the inhalation of asbestos dust, which is produced abundantly during the preparation of the mineral for the spinning process (purification and removal of stony impurities) and during various other phases of the production and manufacturing processes of asbestos and asbestos containing goods. Direct contact of the skin with asbestos is of minor importance. The number of actually exposed persons is rather large in the industries manufacturing asbestos products. Of the 12,000 workers employed in the major asbestos plants of the United States, Lanza estimates that 10,000 are exposed appreciably to the asbestos dust; while in Germany, where several thousand asbestos workers are present, only a fraction are said to be actually exposed.

Symptomatology: Cutaneous Lesions. The direct skin contact with mined asbestos is responsible for the production of painful warts formed around the asbestos needles, which penetrate the skin of the palms of the hands. The

majority of asbestos miners in the Ural Mountains are said to have on the inner surfaces of the right hand three to five or more papular, non-inflammatory, wart-like formations of round or polygonal shape reaching the size of a pea (Dewirtz). They consist of hyperkeratoses sometimes associated with acanthosis and prolongation of epithelial cell pegs. There is some lymphocytic infiltration in the cutis. Between the cornified masses asbestos needles are found. Many mitoses may be present in the thickened malpighian layer, and large giant cells with centrally located multiple nuclei may be present in this stratum. These lesions will persist unless the asbestos needles are removed. The warts do not exhibit any appreciable proliferative tendencies.

Pulmonary Lesions (Asbestosis). The asbestotic pneumoconiosis, resulting from a prolonged occupational inhalation of asbestos dusts and fibrils, is a condition more serious than the cutaneous manifestations. The first fatality of asbestosis was reported by Murray in 1899. It was not until 1914 that a record of an asbestosis death was published in Germany (Fahr). Fatalities from asbestosis as the main or contributory cause of death were published in the United States by Lynch; Stewart, Bucher and Coleman; and Shull. The Metropolitan Life Insurance Company recorded, between 1924 and 1936, seventeen cases in which asbestosis contributed to the lethal outcome of the main disease.

In Germany there was no appreciable interrelation between asbestosis and tuberculosis of the lung, such as exists regarding silicosis. In England there were 30 cases of asbestosis complicated by tuberculosis in a series of 100 cases of this type of pneumoconiosis reviewed by Wood. Similarly, in the United States a certain relation to tuberculosis was apparent, but the coexistence of the two diseases was not as frequent as in the case of silicosis (Stewart, Bucher and Coleman; Shull; and Lanza, McConnell and Fehnel). The development of a pulmonary asbestosis depends, according to Bauer, upon the duration and degree of exposure to asbestos dust, and on a certain personal disposition. A similar observation was made by Sweany, who remarked that some people develop an asbestosis rapidly, while others may be exposed to the same conditions for years without detriment. Individual differences in the filtering qualities of the nasal passages are mentioned by Lehman as possible reasons for such discrepancies in susceptibility.

Asbestosis usually develops after an exposure of three to fifteen years (Martz), but may not produce subjective symptoms until many years after the cessation of exposure to asbestos material. The first symptoms are dyspnea and a cough with expectoration. Later there is pallor, cyanosis, palpitation of the heart, loss of appetite and weight, and piercing pains in the chest during breathing. The shortness of breath becomes aggravated during physical exertion. In the beginning the physical examination reveals scarcely any pulmonary changes; but later there appears a diminution of resonance, especially over the lower parts of the lung (particularly the right side), where dry and

crackling sounds are perceptible in auscultation. The respiratory capacity is decreased, and there is a diminution of the respiratory shift of the pulmonary borders during respiratory movements of the lung. The heart is often enlarged due to the increased functional demand placed on it, because of the decreased respiratory surface and impaired circulation in the lung caused by the pulmonary fibrosis. The enlargement of the right side of the heart becomes accentuated as a cardiac insufficiency ensues. The roentgen-examination of the chest shows an early, diffuse, interstitial fibrosis having reticular honeycomb-like outlines and showing progressive tendencies, which later cause a filmy-hazy appearance of the lung. This condition has been termed "ground glass" appearance. The hilum shadows are enlarged in the more advanced stages. The movements of the diaphragm are reduced. The microscopic examination of the sputum executed with proper methods and thoroughness reveals the presence of golden brown asbestos bodies.

Pathology. The observations made at necropsy reveal a shrunken, blue-black lung of firm consistency containing little air, especially in the lower lobes which often are covered by a thickened pleura. The cut surface shows a widened, thickened, and prominent, interstitial, connective tissue. There are bronchiectases and small abscesses together with pleural adhesions and bronchopneumonic foci. The hilum nodes are enlarged, hard, and brownish.

Upon histological examination asbestos bodies are found in the interstitial connective tissue, and the peribronchial and hilum lymph nodes. These characteristic formations consist of a central translucent fiber or needle-like crystal (asbestos crystal) measuring 10 to 100 microns in length and 1 to 12 microns in thickness. The central fiber is ensheathed in a shiny golden or brown substance with varying architectural figuration. The whole body may have the shape of a rod with smooth blunt ends, or with one or both ends forming a single knob or a conglomeration of knobs. The shaft is often a series of rounded beads or discs strung closely along the central filament (Lynch). In other instances the asbestos body has the shape of a hoe or a club, or represents a long slender filament. The bodies give a characteristic Prussian blue reaction, which is attributed to their iron content. The iron content of the asbestos bodies is higher than that of the asbestos needles. The assumption has been made that the additional iron originates from decomposed erythrocytes. The nature and chemical composition of the asbestos body is still uncertain. McDonald advanced the theory that the central part of the body is represented by a particle of an asbestos fiber in the process of alteration and absorption by hydrolysis, while the enveloping matter was supposed to consist of silica in a colloidal or gel-like state. This latter conception was proposed, also, by Koppenhofer.

Beger contended that the sheath was composed of proteinic matter. The asbestosis bodies are found within the bronchioli, in the alveoli, and in the interlobular, peribronchial and subpleural tissues among the lymphatic routes.

They occur, moreover, in the peribronchial lymph nodes, within the walls of the sinuses, and embedded in fibrous areas. In the alveoli they are surrounded by phagocytic, mononuclear cells and foreign body giant cells massed especially around the larger bodies. The interstitial tissue shows a diffuse fibrous thickening and scarring. The asbestosis is, thus, an indurative, interstitial, diffuse fibrosis of the lung increasing in degree from the apex to the base.

Asbestosis and Carcinoma of the Lung. It is only in very recent years that serious consideration has been given to the possibility of a cancerigenic action of asbestosis upon the lungs. In an analysis of 18,280 death certificates for cancer of the lung and larynx in males from England and Wales from 1921 to 1932, Kennaway and Kennaway did not find any cases of lung cancer in asbestos workers. Since 1935, an appreciable number of cases of asbestosis associated with carcinoma of the lung, have been reported from England, Germany, and the United States (Lynch and Smith; Lynch; Gloyne; Wood; Horning; Nordmann; and Egbert and Geiger). The incidence of lung cancer among workers in whom an asbestosis was found at autopsy is relatively high, ranging from 17 per cent (Nordmann: 2 out of 17 cases) to 20 per cent (Wood: 2 or possibly 3 out of 12 cases). Teleky noted that there exists a minimum of 39 and a maximum of 78 autopsies in fatalities from asbestosis, the records not being clear in this respect. Teleky only knows of 6 cases of pulmonary cancer with asbestosis, and feels that this ratio is high in comparison to the number of necropsies. Koelsch mentioned the occurrence of 12 cases [Lynch (3); Egbert and Geiger (1); Gloyne (2); Dominici (2); Baader (1); Nordmann (2); Wood (3); and Horning (1)]. Lynch and Smith found among 35 autopsies with asbestosis 2 cases of pulmonary malignancy (six per cent), whereas there was an incidence of only 0.3 per cent of this type of neoplasia among approximately 2,300 autopsies of the general population. The period of occupational exposure to asbestos dust ranged for five cases from 7 to 21 years, but in an additional case only a year and a half. In several instances the lung tumor became manifest several years (10 to 12) after cessation of the work in asbestos. Fifteen to twenty-one years elapsed (average, 18 years) between the first exposure to asbestos and the death from asbestosis with carcinoma of the lung. The age at death depended upon the age of the individual at the time of the first exposure. The workers dying in the more advanced age groups entered an occupation with an asbestos hazard later in life, while those who died at an early age started to work in asbestos plants when still young. There was no evidence of a so-called old age predisposition, as two of these cases died at the age of 35 years and a third was 41 years old.

The majority of neoplasms were cornified squamous-cell carcinomas. Only one case was an adenocarcinoma, and a second was an anaplastic, round-cell carcinoma. The latest case reported by Lynch and Smith showed squamous cellular and glandular carcinomatous structures. This numerical distribution between the different histologic types of carcinomas varies distinctly from

that usually observed (Nordmann), but agrees with the shift toward a more frequent occurrence of the cancroids noted in recent years by Probst in pulmonary malignancies of unknown genesis. A multicentric development of malignant growths in asbestos lungs was found by Nordmann and Gloyne, and it is considered by Nordmann as a characteristic feature of this type of lung cancer. A multifocal sprouting of squamous cells lining the bronchial walls was seen by Nordmann, who regards these changes as precancerous in nature. A diffuse, proliferative thickening of the bronchial epithelium was recorded by Gloyne, who believed that this constituted a continuous prolongation of epithelial growth from some unknown starting point rather than a series of isolated proliferative units. These epithelial prolongations were hollow in places, showing a degenerating layer of cells surrounding a central empty space, and, in turn, being enveloped by rings of keratinized squamous cells. The carcinomas of three cases were very small [Gloyne (2); and Nordmann (1)], and had not produced any metastases. For this reason two of these cases (Gloyne) represented coincidental observations made during the post-mortem examination. The other cases were large tumors with extensive metastatic deposits in remote organs.

An evaluation of the evidence presented reveals certain features connected with these cases, which are suggestive of an occupational causation. There is an incidence of lung cancer in asbestosis of the lung which is definitely excessive. The relatively small number of necropsies on which this conclusion is based represents an urgent indication for more extensive post-mortem examinations in cases of asbestosis; especially considering that pulmonary malignancies seen in previously reported cases were, in several instances, very small and were coincidental observations. A second point favoring an industrial origin is the young age of an appreciable portion of the cases thus far recorded, and the relationship existing between the time of exposure to asbestos dust and the manifestation of the neoplasms throughout the entire series. The third factor consists in the shift of the histological types observed in the direction of a predominance of cancroids, and in the multicentric development of two (Nordmann; and Gloyne) and possibly even three (Lynch and Smith) of these pulmonary neoplasms. The existence of the cutaneous warty lesions suggests that asbestos needles embedded in epithelial tissue are apparently capable of eliciting non-inflammatory, epithelial proliferations. Nothing is known about the actual causative mechanism through which asbestosis may produce such epithelial lesions, and may transform them subsequently into malignant growths. The assumption of a chronic irritation of nonspecific nature or of specific silicotic character, such as proposed by Lynch, is scarcely acceptable and satisfactory in view of the negative evidence available in this respect. One of the cases reported by Nordmann in association with Horning showed symptoms of a marked and generalized, allergic disposition (bronchial asthma, and hematic eosinophilia), which may have played a

contributory role in the development of the neoplastic response. Asbestos bodies contain a considerable amount of iron, and there exists some evidence that points to a possible causative interrelation of pulmonary siderosis and carcinoma. The relatively small number of asbestosis carcinomas of the lung reported does not disprove an occupational origin of this condition. Previous experience with other industrial neoplasms (lung cancer of the Joachimsthal miners; and lung cancer of the chromate workers) has shown that such isolated cases may represent the first warning of a subsequent appearance of large numbers of similar tumors of undeniable occupational derivation.

Medico-Legal and Social Aspects. Asbestosis carcinoma of the lung is not included in any group of occupational tumors recognized by any country. The evidence presented is sufficiently serious, and the number of persons exposed to the suspected causative agent large enough to indicate a thorough and extensive clinical, statistical, and experimental investigation of the incidence and causative interrelation of asbestosis and pulmonary carcinoma. In view of the fact that several of the states with many large asbestos plants do not include asbestosis among compensatory occupational diseases, this study is even more urgent. Such a condition militates against an effective hygienic control of an important industrial hazard, and impedes the collection of pertinent and essential information in regard to the incidence, nature, and potentialities of an occupational disease growing steadily in general significance. Workers dying from asbestosis should be subjected to a post-mortem examination including a histological study of the pulmonary lesions, as multiple neoplastic manifestations in asbestosis may be mistaken for tuberculosis (Lynch).

Sanitary Measures. The following measures may be taken to eliminate or reduce the existing hazard caused by the inhalation of asbestos dust: humidification of the asbestos matter and the air to decrease the production of dust; introduction of a closed production system, wherever possible; establishment of an extensive and efficient exhaust ventilation; frequent cleaning of the workrooms to remove the accumulated dust; prevention of air currents caused by moving machinery parts; construction of rooms, machinery, and pipelines offering little opportunity for deposition and accumulation of dust; separation of operations in which the production of dust can be eliminated entirely from those in which this is not possible; wearing of respirators by workers engaged in dusty operations; and mechanization of operations under elimination of human labor to reduce the number of workers exposed. The dust hazard is most pronounced in store rooms for raw material, in rooms in which the raw fibers are handled, and in spinning, weaving, mixing, and filling rooms.

Siderosis

Occupational siderosis of the lung is of the black type, which is caused

by the deposition of metallic iron in the lung, or of the red type, which is the result of the inhalation of iron oxide (hematite) dust (Hart). The black type of siderosis is associated as a rule with a silicosis, as the metallic iron dust is produced during the polishing or grinding process of iron parts in which sand blasting is used. The red type of pulmonary siderosis occurs mainly in hematite miners, especially those engaged in pneumatic drilling. Other miners, also, are exposed, as large amounts of dust are produced in the mines by frequent blasting. The hematite ores contain, in addition to ferric oxide, approximately 12 to 13 per cent silica (Bohrod; and Stewart and Faulds). Ferric oxide is used for the polishing of metal parts, such as screws, in the watch industry in Switzerland (Dreyfuss). Iron dust is not a biologically inert dust (Gardner), as a considerable number of fatalities have been placed on record as the result of occupational pulmonary siderosis, which is characterized by interstitial fibrosis and pulmonary arteriosclerosis.

The existence of a causal interrelation between pulmonary siderosis and primary carcinoma of the lung is suggested by several observations. Metal grinders have an excessive incidence of pulmonary malignancy (2.25 fold of that of the general population), according to Kennaway and Kennaway. The same conclusion was reached by Turner and Grace as well as Campbell. The three cases of lung cancer discovered by Vorwald and Karr among 15,587 workers roentgenologically examined at the Saranac Laboratory were iron miners, one having a silicosis, while the other two were negative for silica. Their ages were 59, 64, and 68 years, respectively, and the period of occupational exposure to hematite dust was 27, 35, and 43 years, respectively. The occurrence of a carcinoma of the lung in a boy, 19 years old, who had been engaged in sand blasting metal parts in an automobile factory was reported by Simons. Two similar cases were recorded by Dreyfuss. This investigator observed a pulmonary carcinoma in two members of a family (brother and sister), which developed twenty-four years after their exposure for twelve years to the inhalation of iron oxide (Fe_2O_3) dust, which was used by their mother at home for the polishing of screws. While the number of lung carcinomas after an occupational inhalation of iron dust is at the present time still small, the evidence presented is considered of sufficient significance to warrant further study as to the actuality of causal interrelations. Some experimental support of the existence of such a relationship was recently provided by Campbell, who found an increase in the lung tumor incidence of mice dusted with iron oxide ($Fe_2O_3 \cdot H_2O$).

Arsenic

In view of the notoriety arsenic has attained as a carcinogenic agent the studies of Saupe, in regard to pulmonary cancer in arsenic workers, are of interest and importance. This investigator examined workers employed in an arsenic ore smelter at Freiberg in Saxony. These men were exposed to

arsenic fumes as well as arsenic dust, and showed evidence of chronic arsenic poisoning. The type of exposure was as follows:

The ground arsenic ores release, through roasting in ovens at a temperature of 220° C, the volatile arsenic oxide (A_2O_3), which is passed into an extensive cooling and condensation system consisting of ducts of brick construction, where this substance precipitates as a white to yellow red powder. These condensation canals are entered by workers every three weeks for the removal of the arsenic oxide, which is shoveled into barrels and shipped to other manufacturing establishments for the production of arsenic acid, dyes, insecticides, medicinal preparations, stained glass, depilatory of hides, and lead alloys.

There were 40 to 50 men engaged in this work at Freiberg. They wore special clothing and carried sponges in their mouths for protection against the inhalation of arsenic dust, made nasal douches, placed plugs of clay into their nostrils as an additional means of precaution, and took baths at the end of the shift. The men who were exposed mostly to the inhalation of arsenic fumes and dust were those attending the roasting ovens, in which molten ores were stirred with poles, those engaged in the cleaning of the condensation canals, and those employed in the manufacture of red glass and metallic arsenic.

Of the forty workers examined by Saupe, all except nine had developed a dermatitis after the cleaning of the canals. Several showed small hyperkeratoses, two had a marked arsenic melanosis, while 57.5 per cent revealed perforations of the nasal septum, and 22.5 per cent had nasal ulcers, similar to those seen in chromium workers. The examination of the chest showed mild pneumoconiotic changes in twelve workers. Two of these workers have died with carcinoma of the lung associated with pneumoconiosis. Saupe concluded that the evidence did not permit a decision as to whether or not these pulmonary malignancies were the result of an occupational exposure to arsenic.

There exists an additional case of carcinoma of the lung in which a preceding prolonged contact with arsenic was present (Frommel). The person afflicted was 46 years old and had used powdered arsenic for the preservation of pelts in his profession as a taxidermist.

The experimental results obtained by Cholewa, who fed 20 white mice with a diet containing arsenic oxide and found carcinomas of the lung in two mice after a period of one year, are of equally uncertain significance, as an incidence of 10 per cent pulmonary tumors is not an unusual occurrence in normal mice more than one year old.

The evidence, available at the present time, is by far too meager to permit any definite conclusion. It appears fair to state under the existing circumstances, that the possibility of a causal relation between the inhalation of arsenic dust and the development of pulmonary malignancy may be conceded, but the probability of such a relationship is small. In view of the constantly increasing industrial and general environmental hazard from arsenic in dust form

(sprays and powder used as insecticide in agriculture), this potentiality deserves increased attention in the future. This warning seems to be especially warranted, as Nieberle recently reported the endemic occurrence of adenocarcinoma of the nasal sinuses in sheep kept on a large estate in Saxony within the fume and dust zone of arsenic smelters of Freiberg. As arsenic was found in the tumor tissue, in the brain, and liver, and attacks of acute arsenic poisoning were frequently observed among members of the herd in which these carcinomas were found, Nieberle suggested that the inhalation of arsenic dust was responsible for the nasal malignancies.

Chromates

Chemical and Technological Aspects. Chromium and its numerous compounds have entered only recently the field of large scale production. They have found extensive use in industry. Chromium is a metallic element of white color, possessing valences ranging from two to six. It does not occur free in nature but mainly in the form of trivalent or hexavalent ores [ferrous chromite, $Fe(CrO_2)_2$ $FeOCr_2O_3$ (United States, Rhodesia, and India), crocoite ($PbCrO_4$), chrome ochre (Cr_2O_3), and as potassium chromates, redingtonit, phospho-chromates, and ferrous thiochromite].

Metallic chromium and numerous industrially used chromium compounds are in general obtained from chemical processing of alkali chromates and dichromates (sodium and potassium compounds). The chief source of these chromates and dichromates is ferrous chromite ore. The mined ore is first crushed and ground to a powdery form. This chromate flour is heated in an oven with the exclusion of air, and then roasted together with sodium carbonate or potassium carbonate, respectively, in the presence of lime. The resulting compounds are chromate salts of sodium or potassium, respectively ($4\ FeCr_2O_4 + 8\ Na_2CO_3 + 7O_2 \rightarrow 2\ Fe_2O_3 + 8\ Na_2CrO_7 + 8\ CO_2$). The molten mass is then cooled and again heated after addition of water and soda. The lime and iron are then filtered off, and the remaining material is treated with sulfuric acid. Upon evaporation of the liquid parts the dichromate compound crystallizes out. This product is dried and crushed and is then ready for industrial use.

The industrial and commercial importance of chromium and its compounds is considerable and growing at a rapid rate. Chromium is used widely for electroplating of metal parts, in the production of various alloys, especially with steel (stainless steel). Chromic acid or usually chromium trioxide, potassium or sodium chromate and bichromate, and chrome alum are used in the manufacture of chromium pigments, as dye mordants, for tanning of hides, for the manufacture of aniline dyes, of colored crayons, inks, colored paper, artificial colored flowers, colored glass, blue print making, calico printing, frosting and enameling, explosives, bleaching of oils, tallow and fat, staining of wood, in photography for making gelatine insoluble, for manu-

facture of water resistant glue and cement, in the production of linoleum, ceramics, rubber tires, electric storage batteries, matches, chemicals, and most recently for the sterilization of drinking water (Akatsuka and Fairhill) in place of the usual treatment with chlorine.

Toxicological Aspects. In view of the rather recent large scale production and consumption of chromium and its compounds, these substances became of importance from the standpoint of industrial hygiene and toxicology only in the last several decades. While metallic chromium is nontoxic, chromium compounds are poisonous in varying degrees. The hexavalent chromium compounds are more toxic than trivalent ones. The hexavalent compounds are transformed into trivalent compounds in the presence of organic matter in the course of several hours, unless substances are present which interfere with this reaction. The local effect of chromium compounds, especially of alkaline chromates and bichromates, is a corrosive one and is exerted mainly upon the skin and mucous membranes of the upper respiratory and alimentary tract. The cutaneous manifestations consist in dermatitis and ulcerations (chromium holes) which show little tendency to heal. Chromium compounds are fixed at the point of contact by forming a protein complex, which is not hydrolyzed readily. The skin of the forearms, hands, and legs is affected chiefly. The end results of such chromium holes are deep cicatrices. The inhalation of chromate dust, fumes, or vapors generated during the mining of chromium ores and in the production and handling of chromium compounds results in multiple smaller ulcerations in the buccal cavity, tonsils, pharynx, and, particularly and characteristically, in the nasal septum. There occur inflammatory conditions of the upper and lower respiratory tract (rhinitis and bronchitis), which may lead ultimately to the development of pulmonary fibrosis.

Systemic chromium poisoning of occupational origin is exceptional in spite of an often intense exposure of the workers to chromium compounds in the form of dust, fumes, vapors, or in solution. The symptomatic manifestations observed in such isolated cases were those of asthma and nephritis (Smith; and Delpech). Systemic effects experimentally produced in animals by the introduction of chromates consisted of respiratory, digestive, and nephritic disturbances.

Chromates possess a marked tendency to produce sensitization of certain organs (skin, lung, and kidneys), resulting in the production of allergic dermatosis, bronchial asthma, or nephritis (Card; Smith; and the International Labour Office). Acute attacks of chromium allergy may be accompanied by a marked hyperleucocytosis (32,760) in addition to cutaneous and renal manifestations (Smith). In a case of chromium asthma, observed by Card, this condition developed after 5 months of work in chromium plating. The subcutaneous injection of 4 mg. of potassium bichromate elicited in this person an acute asthmatic attack, without causing any cutaneous reactions, such as is usually seen in response to the cutaneous introduction of allergens. It is

thought that the adsorption of small amounts of a chromium compound through the skin, lung, or gastro-intestinal tract over a prolonged period leads to dysfunctional phenomena, caused by a sensitization of the organism to chromate-protein complexes.

Lung Carcinoma in Chromate Workers: Incidence. A carcinogenic action of chromates has been denied for many years (Lehmann). Constant irritation exerted by chromium compounds on the skin and mucous membranes of the mouth and nose has never started an epithelioma in spite of the production of chronic ulcerations and the active destruction of tissues (Legge). The irritative action of chromium compounds seemed to lack, in the opinion of White, some specific qualities as they do not exert any proliferation stimulating action. On the basis of these observations White advanced the conception that malignancy was not merely the result of an irritation of some nonspecific acute or chronic inflammation, even if the irritation was often repeated or continued. In support of this conception Legge reported in 1922 that there were 175 cases of chrome ulceration on record in the English industry (93 in the manufacture of chromates; 69 in dyeing operations; and 7 in chromate tanning), but none of them gave any suggestion of epithelioma. This optimistic outlook was destroyed definitely in recent years by the demonstration of an excessive incidence of pulmonary malignancy among workers of several German chromate factories.

This development had been foreshadowed many years before by the occurrence of a few isolated cases of malignancy of the respiratory tract in chromate workers. The suspicion as to an occupational origin of these neoplasms expressed at that time was not given any credence. The first instance of a carcinoma of the respiratory tract in a chromate worker was recorded by Newman in 1890 (Scotland). This investigator found a large adenocarcinoma originating from the nares of a man, 47 years old, who had been employed for 20 years in a chromate plant and who had, as the result of his occupation, the characteristic perforation of the nasal septum. More than twenty years later (1911 and 1912) Pfeil observed two additional cases of malignancy in chromate workers, this time located in the lungs. These workers were employed in a German plant, in a chromate operation, in which alkaline chromates were produced or used in the manufacture of quinones. These two cases of pulmonary carcinoma in chromate workers remained unique for many years. When in 1932 Lehmann commented upon their occurrence in connection with a discussion on occupational pulmonary malignancy, he was still convinced that no etiological connections existed with an occupational exposure to chromates, as no additional cases of pulmonary carcinoma had been noted since 1912. There was no reason for any undue alarm at that time, in his opinion.

Any doubts which had existed in this respect were removed definitely only three years later by the communications of Pfeil (1935); Alwens, Bauke

and Jonas (1936); Teleky (1936); and Gross (1936), who reported the occurrence of an appreciable number of lung carcinomas among workers of several chromate plants. There were five additional cases observed by Pfeil among workers of the chromate plant (Ludwigshafen), in which the first two cases, recorded by Pfeil, were found. A total of 10 cases of bronchial cancer, occurring from 1926 to 1936, was traced by Alwens, Bauke and Jonas to a chromate factory in Griesheim. These investigators became suspicious for the first time in 1929 concerning a chromate etiology of some of their cases of pulmonary malignancy, which came under their care at Frankfurt. Jonas diagnosed 5 additional cases from roentgenologic evidence among the workers employed in the same plant. Gross mentioned the occurrence of several sporadic cases among the workers of some other chromate plants (Uerdingen, Bitterfeld, and Leverkusen). Up to 1936, 25 cases of pulmonary carcinoma among chromate workers were placed on record (Koelsch), and this number has increased since (Bauer). The majority of cases observed so far have occurred among workers of chromate plants, which had been closed for some time (Ludwigshafen in 1923 and Griesheim in 1931). No cases of pulmonary malignancy have been noted, as yet, among the workers of chromate factories erected more recently (Teleky). This investigator gained, moreover, the impression that the incidence of gastro-intestinal cancers was excessive among chromate workers. His data, in support of this assertion, are insufficient for any definite decision.

Causative Mechanism. The etiological agent and the causative mechanism involved in the production of the pulmonary carcinomas in chromate workers are still entirely unknown. Attempts which have been made by Teutschlaender and Gross to reproduce these tumors in animals by an exposure to the inhalation of chromate dust were unsuccessful. There was only a swelling of the hilum nodes attesting to the irritative effect of the chromates. Similar results were reported by Lukanin, who exposed rabbits and cats to the inhalation of dust from chromium ores and from chromates. With the exception of emphysema, interstitial pulmonary fibrosis, and the deposition of a brown pigment (iron chromium ore) nothing was observed even suggesting preneoplastic pulmonary lesions. One of the rabbits had a perforation of the nasal septum. These changes were identical with those observed by Lukanin in a chromium ore miner, who had been killed in an accident after an employment of 5 years.

Many of the workers affected were employed in a chromate operation in which they inhaled, in addition to large amounts of ferrous chromite dust, dust of chromates and chromate fumes. Other workers afflicted with pulmonary tumors had been engaged in the production of sulfuric acid (3), hydrochloric acid (1), and sulfates, and in the regeneration of chromic oxide to chromic acid from the oxidation bases used in the manufacture of quinones. Several other workers were listed as drivers (2), glaziers (1), welders (1),

and smiths (1); but all of them had worked near chromate operations and had been exposed to the same agents as the chromate workers proper, or they had been employed for some time previously in this operation and thus had established a direct occupational contact with chromates. One case of chromate lung cancer, reported by Baader, was not found in a chromate worker but in a man who had sprayed chromate dyes from a spray gun for a number of years.

The inhalation of dust from chromium ore was considered by Koelsch as innocuous in regard to carcinogenesis, as this compound is relatively insoluble in the body fluids. In his opinion, this compound cannot interact very readily with the cellular and liquid component parts of the body. This investigator believed that a prolonged inhalation of bichromate dust and fumes is to blame for the production of pulmonary malignancy. The irritative effect of these agents upon the bronchial epithelium was said to cause an epithelial hyperplasia, which in the long run becomes malignant. Similar conceptions were expressed by Alwens, Bauke and Jonas; Teleky; and Pfeil. In support of his contention Koelsch pointed out that chromium was found in the lung of one case of pulmonary cancer in a chromate worker. This observation was substantiated recently by Alwens. The actual value of such an observation may be estimated by recalling that Dingwall and Beans, using the spectrum arc method, found, several years ago, abundant amounts of chromium in an appreciable number of benign and malignant tumors of various types and of cryptogenetic origin. As it scarcely can be claimed that chromium is a rather universal carcinogenic agent, the presence of chromium in lung tumors of chromate workers loses much of its alleged, etiologic significance.

The actual carcinogenic mechanism has remained uncertain, but it appears unlikely that a chromium compound, as such, is the carcinogenic agent. It seems to be more probable, considering the chemical nature of the known carcinogenic agents and their relations to biological aromatic substances of hormonal, biliary, or vitaminic nature, that chromium compounds may act on some of these naturally occurring chemicals in such a way that carcinogenic agents result. Some of the reactions, which possibly may be present and which may deserve some consideration in this connection, may be pointed out here. Sodium dichromate exerts a quinogenic action upon certain aromatic hydrocarbons and cyclic amines, such as benzol, naphthalenes, anthracene, phenanthrene, chrysene, flavanthrene, aniline, and pyrrhol. Chromium oxide splits off some of the side chains from some cholesterol derivatives (Fieser), and may give rise to pathological types of cholesterol compounds. Attention may be called to chromium compounds, which are chemically homologous with nickel carbonyl, which is suspected strongly of being involved in the production of another type of occupational cancer of the respiratory organs. There occurs a chromium carbonyl ($Cr(CO)_6$), which is formed by the heating of chromium chloride in the presence of CO and magnesium phenyl bromide. This substance

is homologous to nickel carbonyl ($Ni(CO)_4$) and to iron carbonyls ($Fe(CO)_4$; $Fe(CO)_5$; and $Fe_2(CO)_9$), which are lipoid soluble. While no information is available as to whether chromium carbonyl is formed as a by-product during the manufacture of chromates and what biological qualities this compound possesses, an investigation of these aspects is indicated in view of the analogy with the lung and nasal cancers observed in nickel carbonyl workers. Finally, chromium compounds are apt to give rise to allergic phenomena. They may act as haptens, which in combination with protein molecules may form allergenic agents, or the transformation of aromatic biological substances into quinones may cause these to combine with proteins and produce allergens. This type of causative mechanism may be involved directly or indirectly in the production of these chromate cancers, considering the numerous observations made in regard to the important role which chemical allergies play in degenerative and proliferative, cellular manifestations.

Contributory Factors. Among the contributory causes of pulmonary tumor in chromate workers Koelsch listed personal susceptibility, as only a small fraction of the workers employed in the chromate operations have developed these neoplasms. Individual reactivity apparently plays a role in determining the readiness with which a carcinomatous development ensues in different individuals. Nevertheless, this factor becomes correspondingly less important, as far as the absolute and ultimate incidence of neoplasms is concerned, as the duration and degree of exposure to a carcinogenic agent are increased. No accurate data are available on the absolute incidence of pulmonary carcinomas among workers employed in various factories, as the workers were shifted to other operations when these plants were shut down (Pfeil), and the final fate of some of these men will remain unknown.

Old age was mentioned by Koelsch as a second factor contributing or predisposing to the development of these tumors. It is doubtful whether tissue senescence actually plays a role in this respect, since the exposure time of this type of neoplasm ranges from 22 to 40 years (average 31 years) and only in exceptional instances is much shorter (10 years in one of the cases recorded by Alwens). This fact alone is sufficient to account for the more or less advanced age of the workers when the pulmonary malignancies were discovered (48 to 68 years).

Racial factors evidently cannot be incriminated in the regionally restricted occurrence of these neoplasms. The reasons for this phenomenon may be sought in the differences in production methods and chemicals handled and manufactured from chromate ores in various countries. Also, there may exist marked variations in the medical supervision of workers employed in chromate operations in different countries, and this fact may account for the apparent absence of chromate cancers outside of Germany.

A careful analysis of the family history of the afflicted chromate workers

for the occurrence of cancer, did not reveal any evidence supporting the conception that heredity plays any part in the production of pulmonary malignancy in chromate workers (Alwens).

Symptomatology. The pulmonary neoplastic disease of chromate workers has an insidious beginning. In general, chromate workers develop chronic, inflammatory, irritative conditions of the upper respiratory tract, which may result in the production of nasal septal ulcers and perforations one to two years after entering the plant. During the years preceding the manifestation of the tumor the inflammatory symptoms of the respiratory tract become more pronounced and extend to the lower portions, remaining nonspecific in character. Following a period characterized by frequent and prolonged coughing spells and pains in the chest, there occur attacks of bronchopneumonia and protracted bronchitis. Finally, when pleuritic symptoms appear, they are usually accompanied by definite signs of a neoplastic process in the chest, such as radiating pains, dyspnea, and coughs with expectoration, and the physical symptoms of an infiltrative pulmonary condition (faint breath sounds and crackling râles), indicating the presence of a bronchial stenosis, pulmonary gangrene and cavitation, and hemorrhagic pleurisy. Many of the workers, who developed pulmonary malignancy, showed upon roentgen examination an enlargement of the hilum nodes sometimes affecting only one side. This symptom is considered a precancerous sign in chromate cancer of the lung. The tumor shadow spreads usually from the hilum into the pulmonary parenchyma. The entire clinical and roentgenological picture of chromate cancer does not differ in any essential respect from that seen in the ordinary non-occupational type of lung carcinoma. This identity extends to the differential diagnostic considerations and to the prognosis, which is as unfavorable in chromate cancer as in cryptogenetic carcinoma of the lung.

The tumors were located in 3 cases on the left side, in 11 cases on the right side, and in 1 case on both sides (Alwens). A squamous-cell carcinoma was found in 4 cases, a round-cell carcinoma in 2 cases, and adenocarcinoma in 2 cases, and an anaplastic carcinoma in 1 case. Metastases were present in all instances and, often, were extensive.

Medico-Legal Aspects. Pulmonary malignancy caused by an occupational exposure to chromates is recognized as a compensable industrial disease in Germany, but has not been included in this list for obvious reasons in any other country. Claims for indemnity should be recognized in all instances in which persons have developed cancer of the lung and possibly cancer of the nasal passages, after a prolonged industrial exposure to chromates in the form of dust, fumes, or vapors. Since a carcinoma of the lung was observed in one case after an exposure of ten years, the lower limit of the exposure time should be placed below 10 years (5 to 8 years), and even a shorter period of occupational contact with chromates may be allowed, if it can be shown that the particular claimant is allergic to chromium compounds. For

the demonstration of a hypersensitivity of the skin against chromates by the patch test method, it is essential that high dilutions of chromium compounds are used, as pseudo-positive results may be obtained by the application of more concentrated solutions, which exert a nonspecific irritative effect upon the skin.

Sanitary and Precautionary Measures. A closed manufacturing system should be introduced wherever the exigencies of the work permit such changes. An adequate exhaust ventilation should be installed in all those operations in which the complete elimination of the dust hazard by the closed system is not feasible. It may be necessary, in view of these neoplastic reactions, to readjust the amount of chromate in the air to a lower level than that considered permissible at the present time. The present upper limit of safety for an extended exposure to chromates in the air is fixed arbitrarily at 1 mg. of these substances for 10 cubic meters of air. This is the quantity of air breathed by an adult individual during the course of one day. Installation of shower baths, and the wearing of masks or respirators, and rubber gloves by the workers should be insisted upon, where direct contact with the chromates cannot be eliminated (Uyttendoeff). A careful selection of the workers to be employed in these operations seems to be essential, as all applicants with an allergic history or with positive tests for chromates (skin or lung) should be excluded. Workers should be given thorough physical examinations at least once a year, including a roentgen examination of the chest (Clerf). At these occasions workers showing enlarged hilum nodes should be removed immediately from the operation (Koelsch). It may be advisable to restrict the time of employment of a worker in these operations to three years (Pfeil). The workers should be informed of the dangers to which they are exposed through their work and of the significance of the prophylactic measures taken. Post-mortem examinations should be made obligatory on all workers who have been exposed to chromates during life, in order to reliably ascertain the relative and absolute incidence of pulmonary malignancy among this group of workers.

Nickel carbonyl

Chemical and Technological Aspects. Nickel occurs in nature as a sulfide with arsenic and antimony. The chief sources of nickel are ores, which contain a hydrated silicate of nickel and magnesia ($[Ni, MgO] \cdot SiO_2 \cdot nH_2O$) found in New Caledonia, and iron sulfide ores (ferrous pyrrhotine) having an admixture of nickel and copper, which is mined in Canada.

The large scale production of nickel from these ores as well as the extensive industrial use of this metal, its alloys, and compounds is a development of the last century. The type of technical methods, employed in the recovery of nickel from these ores, depends mainly upon the character of the ore used. The ore mined in New Caledonia is roasted with calcium sulfate or alkaline

waste. The matte thus formed is blown into a Bessemer converter or heated in a reverberating furnace with a siliceous flux, the object being to form a rich nickel sulfide. This sulfide is then converted into an oxide by further heating, and is finally reduced to the state of metal by ignition with carbon in clay crucibles. Smelting plans, using this procedure, have not experienced so far the appearance of malignant neoplasms of the respiratory tract among their workers (Germany).

The process of refining adopted for the treatment of the Canadian ores, which are poor in nickel and contain small amounts of copper, consists in a preliminary roasting of the ore in heaps, followed by smelting the roasted product in a blast furnace together with a siliceous flux for a rich matte. This matte is then mixed with coke and salt cake and melted down in an open-hearth furnace, or in a Bessemer converter with a silicate lining. The refined matte containing copper, nickel, and iron sulfides is then roasted to remove the sulphur. This procedure is followed by an extraction with sulfuric acid, reducing the iron and copper content and increasing the nickel content. A subsequent reduction by water gas at 30°C leaves a mass containing metallic nickel, copper, and iron oxide. During this process the water gas is largely deprived of its hydrogen and becomes relatively rich in carbon monoxide. After passing this modified water gas through a retort of hot coke to raise the proportion of carbon monoxide, the gas is passed over the finely powdered (in ball-mills), metallic nickel-copper mixture at a temperature of about 86°C. The nickel combines with the carbon monoxide and forms the volatile nickel carbonyl ($Ni(CO)_4$), which contains a minor admixture of iron carbonyl ($Fe(CO)_5$). The vapors of the two carbonyl compounds are passed through towers at a temperature of 180-200°C, where the nickel is often deposited in pellets of pure nickel, while the liberated carbon monoxide is used again (Mond Process) (*Encyclopedia Britannica;* Stephens; and Ullmann). The workers engaged in this operation are exposed to the inhalation of dust from the powdered nickel ore and vapors of nickel carbonyl, a substance, discovered by Mond, Langer, and Quincke in 1890. Carcinomas of the nasal passages and of the lung have occurred among these workers. English and American plants use this process.

Toxicologic Aspects. Metallic nickel and a great majority of its compounds are relatively non-poisonous. However, the human skin becomes sensitive rather readily to nickel and its salts. Nickel eczema is a frequent occupational disease, affecting from 60 to 90 per cent of the workers coming into contact with these substances for periods exceeding several weeks (Blaschko; Schittenhelm and Stockinger; Kolzow; Dubois; Burckhardt; Sources and Ball; and Weber). While Jadassohn and Schaaf did not succeed in producing experimentally a hypersensitivity to nickel in man, Walthard produced this condition in guinea pigs.

Nickel carbonyl is extremely toxic (Amor). Acute poisoning with nickel

carbonyl in man, a rather frequent occurrence among workers of the Mond plant but reputedly eliminated since 1904 (Armit), is characterized by the appearance of pulmonary edema and hemorrhages as well as cerebral hemorrhages. Similar effects were observed by Armit in rabbits, cats, and dogs exposed to nickel carbonyl. In addition to the pulmonary and cerebral lesions, there were, in the animals, hemorrhages of the upper air passages, in the suprarenals, and, less often, in the kidney, spleen, and liver.

The cause of the high toxicity of nickel carbonyl is still unsettled. Nickel carbonyl inhaled into the lung is disintegrated, according to McKendrick and Snodgrass, at the site of contact with the pulmonary tissue. The nickel is deposited in the lung, while the carbon monoxide released can exert its toxic action upon the system. These investigators believe that at least a part of the toxic effect of nickel carbonyl is attributable to the carbon monoxide freed in the body. A different explanation is proposed by Vahlen, who determined the carbon monoxide content of the blood of dogs poisoned with nickel carbonyl, and found that nickel carbonyl is much more toxic than carbon monoxide. This investigator concluded that the toxicity of this compound depended upon the action of the entire molecule. Armit attributed the high toxicity of nickel carbonyl to the fact that this compound is decomposed in the lungs, and forms a new substance which is precipitated in the pulmonary tissues. This unknown compound releases nickel in gaseous form, which supposedly possesses a special affinity for the brain and suprarenals. The toxic action of nickel carbonyl is due to these qualities, and is not caused mainly by the release of carbon monoxide, according to Armit.

Bayer, who studied two fatal cases of nickel carbonyl poisoning of man, concluded that this substance acts as an inhalation toxin on the large surface of the respiratory epithelium. It produces a toxic pneumonia, with simultaneous involvement of all parts of the lung, characterized by a peculiar coagulation process of the lung tissue.

Nickel carbonyl is a colorless, mobile liquid which is readily soluble in alcohol, ether, benzol, chloroform, and other organic solvents. While only small amounts of this compound can be dissolved in water, it forms an emulsion with water. Its solubility in serum, however, is twice as high as that in water, and it is taken up easily by fats. The presence of nickel carbonyl in the blood can be demonstrated by spectroscopic methods (Kötzing). Approximately 75 per cent of the nickel carbonyl introduced into the body is eliminated with the urine (Armit).

Carcinoma of the Nasal Passages and Lungs. The first report concerning the occurrence of an excessive number of carcinomas of the nasal passages and of the lungs among workers of the Mond Nickel Company, employed in the Clydach plant, South Wales, was made by Grenfell in 1932. The first appearance of these tumors was noticed in 1924 (Baader). There had been observed, during the eleven years preceding 1932, eleven cases of cancer of

the nasal passages with nine fatalities. This fact was confirmed by a brief statement issued by E. H. Cooper, the physician of the Mond Nickel Company in 1933. During the same year, Stephens reported that these tumors occurred among workers handling the Bessemer matte. The condition started, according to this investigator, with an irritation of the nasal passages followed by an inflammatory condition. Turbidity of the antrum and the ethmoid cells were early signs of a preneoplastic or neoplastic involvement of these tissues. Papillomas or polyps were formed, often originating from the ethmoid cells. These proliferative reactions became malignant ultimately, and tended to invade the orbit and the frontal sinus. Of a series of sixteen cases, thirteen were polymorphous-cell carcinomas and three were squamous-cell carcinomas (Baader). The exposure time of the workers was, on the average, twenty-two years.

In spite of extensive and marked improvements directed toward the suppression of dust and fumes, made in the plant during recent years, a considerable number of additional cases of respiratory malignancy occurred among the workers. Between 1932 and 1936 there were 20 new cases of cancer of the nasal passages, 19 of which proved fatal, and 19 carcinomas of the lung, 17 of which terminated in death (Bridge). These cases could be traced to two nickel refineries in South Wales. An analysis of the death certificates issued in South Wales showed that 36 cases or 34.2 per cent of the 105 cases of cancer of the respiratory organs, which occurred between 1907 and 1934 among the population of the district in which the nickel refineries were located, were copper-nickel refinery workers.

The etiological agent and the causative mechanism responsible for the production of these tumors have remained a matter of speculation. The inhalation of nickel carbonyl might be involved in the etiology of these occupational neoplasms. From our present knowledge of chemical carcinogens it does not appear probable that this compound possesses primary carcinogenic properties. If nickel carbonyl can be incriminated at all in this connection, it seems more likely that its biological action on the various component parts of the tissue in contact with it produces substances which may display such qualities. Reference may be made to a reaction of nickel carbonyl with aromatic hydrocarbons (benzene). Nickel carbonyl changes benzene into anthracene derivatives in the presence of aluminium chloride at a temperature of 100°C. It is not known if nickel carbonyl may perform similar changes with the benzol group of compounds in the living organism. Finally, nickel compounds apparently form combinations with proteins, which are evidently the cause of the chemo-allergies observed in nickel workers.

Various Noxious Gases and Fumes

A great number of noxious fumes, vapors, and gases of non-aromatic character have been incriminated, during more recent years, in the production

of tumors of the respiratory tract. Inhalation of fumes from inorganic acids and alkalies in chemical plants and laboratories are mentioned in this respect by Kikuth, who observed a pulmonary cancer in a chemist; while Hünermann reported a laryngeal carcinoma after such an exposure. Koelsch, in a study of 100 workers employed in plants manufacturing various acids (hydrochloric acid, sulfuric acid, and nitric acid), could not find a single case of lung cancer and made an identical observation among workers of the acid consuming (chemical, metallurgic, and graphic) industries. Betke recorded in 1933 three cases of lung cancer in workers exposed to fumes of sulfuric acid and hyrochloric acid after an exposure of 28, 31, and 42 years, respectively. The experimental production of lung tumors by the intrabronchial insufflation of hydrochloric acid into rabbits by Winternitz, Smith, and McNamara was unsuccessful, as only atypical, epithelial proliferations resulted.

A few cases have been reported in which organic, non-aromatic gases, and vapors have been incriminated in the production of tumors of the respiratory organs. The development of a laryngeal carcinoma, allegedly caused by the caustic action of benzine-petroleum vapors inhaled for a period of three years, was reported by Birkholz. The claim made by Stephens that the inhalation of carbon monoxide, contained in industrial waste gases and in the exhaust gases of automobiles, was responsible for the recent increase of lung cancers was investigated by Campbell, who exposed mice to the prolonged inhalation of carbon monoxide. This treatment did not cause any increase in the normal lung tumor incidence among the mice used, and it even retarded their growth.

The alleged carcinogenic action of war gas poisoning has played a conspicous role among speculations as to the cause of the recent increase in respiratory malignancy. Gas poisoning by chlorine, phosgene, diphosgene, dichlorethyl sulfide, and thioglycol chloride has been considered one of the possible major causes in this development by Kikuth; Brockbank; Goltz; Klotz; and Derischanoff. Residuals of warfare gassing were noted by Matz in 10 out of 138 cases of pulmonary cancer among American World War veterans. 4 out of 64 cases, recorded by Brockbank, were gassed badly during the war. Woelsch conceded that a few cases of lung carcinoma exhibited a doubtful etiological relation to war gas injuries, he did add that the existence of an individual predisposition must be assumed in these instances as the individuals affected were young, and that these carcinomas represented the result of an acute trauma. This last argument is fallacious, as war gas poisoning produces chronic, pathological, pulmonary lesions, such as obliterative bronchiolitis and epithelial, bronchiolar metaplasia, which are looked upon by some investigators as the precancerous residuals of gassing. The development of a laryngeal carcinoma on the basis of an ulcerative war gas injury was noted by Spamer, and a second similar case was placed on record by Tilley (cited by Denker).

These observations and conceptions have not been generally confirmed and accepted. A connection with war gassing was lacking in the series reported by Berblinger; Probst; and Hofman. Nolan could not establish such interrelations from a statistical investigation of the personnel records of the American Expeditionary Forces, and autopsy reports of ex-service men in the United States. From an analysis of the evidence available, Simons concluded that there is little support for this conception and much against it. The increase of pulmonary malignancy observed during the same period in countries which did not join in the war remains unexplained (Probst).

The experimental evidence is either negative or inconclusive. Several hundred dogs exposed for several years to various gases used in gas warfare (chlorine, phosgene, chloropicrine, beta-beta'-dichloro-diethylsulfide, lewisite, and methyldichloroarsine), administered in almost lethal concentrations, did not show any permanent injury to the lungs or bronchi (Koontz). Epithelial metaplasias of the bronchial mucosa were seen by Ricker and Adelheim in animals exposed to chlorine gas and phosgene; while Miller, cited by Koelsch, observed a proliferation of the basal cells of the bronchial epithelium after an inhalation of diphosgene.

It is possible that exposure to some of the various gases, vapors, and fumes mentioned may have contributed to a minor degree to or furnished the last stimulus to the development of pulmonary malignancy in some isolated cases. Yet the evidence at hand does not support the conception that these occupational or environmental factors have assumed any significant part in the rise of the incidence of pulmonary malignancy in recent years.

Tar, Pitch, Mineral Oil, Paraffin, Soot, and Aromatic Chemicals

General Aspects of Exposure. The inhalation of coal dust is not credited in general as exerting a carcinogenic effect upon the respiratory organs (Jordan). A low incidence of pulmonary malignancy (38 to 71) and laryngeal cancer (44 to 58) (general population 100) was found to be present in coal miners by Kennaway and Kennaway. Gough observed a case of lung cancer in one of 6 coal trimmers dying from anthracosis after an occupational exposure of 25 years. The same claim cannot be made in regard to the carcinogenic qualities of the distillation and fractionation products of coal and crude oil, since they contain aromatic compounds.

The constantly increasing use of coal and crude oil for fuel purposes in furnaces and engines, and the employment of their numerous distillation and fractionation products (tar, pitch, creosote, grease, lubricating oil, and fuel oil), for an innumerable variety of industrial purposes, has brought a continuously growing proportion of individuals into close contact (occupational or environmental) with these agents. This exposure is not only of a cutaneous and alimentary nature, but is also of a respiratory type (inhalation of these agents in the form of gas, vapor, fume, mist, or dust), and does not extend

merely to some occupational groups, but to the great masses of people of all industrialized countries. Numerous investigators have incriminated these agents, containing frequently carcinogenic aromatic hydrocarbons, in the production and recent increase of respiratory malignancy (Probst; Katz; Berblinger; Schachter; Brandt; Staehelin; McCrae, Funk and Jackson; and Vorwaldt and Karr).

The respiratory exposure to chemical substances of this character may be the result of a general atmospheric pollution affecting the entire population, it may be connected with some special occupational activities or it may be related to the habit of tobacco smoking. In an appreciable number of people two or three of these sources exert a combined action upon the respiratory organs. In addition to such a direct action of substances containing aromatic hydrocarbons of potentially or suspected carcinogenic nature, a cutaneous or alimentary contact with these substances may result in an activation of genetic qualities, present in some persons, favoring the development of pulmonary malignancy.

Environmental Atmospheric Soot. The general pollution of the environmental air with tar and tarry substances originates from various sources; soot from coal or oil burning industrial or domestic furnaces; tar containing dust from tarred roads; and exhaust fumes from gasoline and Diesel engines. The contamination of the atmosphere with soot is by far the most prominent source of tar particles in the air. This factor is marked in densely populated and industrialized districts, particularly when the weather is apt to be foggy for extended periods, keeping the soot particles suspended in the lower strata of the atmosphere (DesVoeux; DuPlessis; and Editorial, *J.A.M.A.*). A fair conception of the amounts of soot involved under such conditions may be obtained from the following statements: "The average English family creates every year more than its own weight of smoke" (Des Voeux); "four hundred and five tons of deposit from the air were totalled within a year per square mile in Finsbury Park, London" (Campbell); and deposited matter per square decameter per annum (1923) (Kennaway) in grams:

Location	*Tarry Matter*	*Carbonaceous Matter Other Than Tar*	*Total Solids*
Meteorologic Office (London)	295	2,509	13,013
Newcastle-on-Tyne (Industry)	437	4,566	16,796
Rothamsted (Country)	—	668	3,438

In a discussion of the general significance of the smoke nuisance to the health of the population of Edinburgh and East Scotland, Langrishe expressed the opinion that there existed good reasons for believing that tarry matter contained in smoke was partly responsible for the increase of lung cancer in

recent decades. Some circumstantial evidence in support of this conception was provided by Schnurer, through an analysis of the post-mortem observations made in a hospital for indigent patients in the Pittsburgh district, where the air contains much soot from the furnaces of the numerous, large, industrial establishments using soft coal as fuel. The series of 342 autopsies was divided into five groups according to the degree of pulmonary bituminosis present in the individual case. The following relation between the degree of bituminosis and the incidence of cancer of the lung was obtained:

Degree of Bituminosis	*Number of Cases*	*Average Age*	*Primary Carcinoma of Lung*
I	30	37·5	—
II	112	42.71	2 (1.8%)
III	146	55·33	3 (2.05%)
IV	46	59.25	5 (10.8%)
V	8	54.12	—

While there is a certain relation of the incidence of lung cancer to the average age, Schnurer felt that the sudden jump from 4 per cent in group III to 10 per cent in group IV was suggestive of a causal connection of pulmonary malignancy with bituminosis. This conception is supported by the data supplied by H. L. Dunn from the United States Bureau of Census who tabulated all cases of primary lung cancer occurring in the United States from 1930 to 1934. The death rates of lung cancer in large cities were consistently and noticeably higher than those of rural communities (Seelig and Benignus). Such statistical data should be evaluated with great caution and no dogmatic conclusions can be drawn from them. Census figures contain numerous, uncontrolled and uncontrollable factors which make a reliable interpretation of them impossible (the diagnosis of lung cancer is made more frequently in larger cities because of better diagnostic facilities and more extensive use of post-mortem examinations than in rural districts, where on these accounts the diagnosis of pulmonary malignancy will be more often missed).

A second major source of the pollution of the air with tarry substances is by the dust coming from tarred or oiled roads. As the practice of tarring or oiling roads to suppress the dust nuisance is of relatively recent date and becomes continuously more generalized, some investigators have claimed that inhalation of tarry road-dust has a causative relationship to the rise in the incidence of pulmonary malignancy (Staehelin; Probst; and others). Serious consideration must be given to this contention in view of the huge quantities of tar which are used every year for this purpose in all civilized countries (according to Lehmann: Germany in 1924 employed for this purpose 3000 tons of tar; in 1926 there was a rise to 60,000 tons; and in 1927 to 1929 a yearly consumption of 100,000 to 120,000 tons was recorded. England used at that time 700,000 tons yearly). The tar used in Germany is a hard-

coal tar, obtained from gas works, mixed with pitch and tar oils. A potential occupational exposure, entailing the possibility of a neoplastic pulmonary response, exists for road workers applying the tar and for drivers of vehicles (automobiles, cabs, trucks, trolleys), traffic policemen, and venders who may inhale the dust from tarred roads.

While the theoretical, circumstantial evidence evidently favors the conception of a causative relationship between road tarring and lung cancer, actual experience lends little or no support to this contention. There is no appreciable excess in the incidence of lung cancer among the workers engaged in the tarring of roads in Denmark (Husted and Biilmann). A similar observation was made by Lehmann. An increase of lung cancer was absent in France and Sweden in spite of extensive tarring of roads (Vincent; Brandt). Any proven connection between dust from tarred roads and pulmonary carcinoma was disclaimed by Fischer. Pulmonary malignancy, on the other hand, was reported to be on the increase in countries in which tarring of roads was done only exceptionally [(Russia, Jaffé); (Latvia, Konrad and Frank)].

It was pointed out by Kennaway and Kennaway that the quantity of tar contained in the dust from tarred roads was negligible in comparison to the quantity of tar included in the soot released into the air with smoke. Careful examinations regarding the tar content of road dust and of the amounts of dust produced by an automobile moving at various speeds on tarred streets were made by Lehmann, who concluded from his observations that the hazard in regard to pulmonary malignancy was negligible. The amount of tar present in the dust (5 per cent) was too low in his opinion to cause a malignant response of the lung. This investigator contended that the quantity of dust stirred up by a moving automobile on a tarred road was practically nil and that the wear by traffic on the tar covering was relatively small.

These arguments were, however, not accepted by Kling, Samssonov and Héros who noted that benzpyrene contained in the tar adheres to the silica particles and is inhaled, and may, in part, account for the rise of pulmonary malignancy in France during recent years. As a systematic and reliable study on the incidence of lung cancer among persons using tarred roads, living or working on or near such roads, and inhaling their dust outside or inside of dwellings, is non-existent, definite conclusions on the pulmonary hazard from tar contained in road dust must be deferred.

The third major source of importance which causes pollution of air with substances resulting from the combustion of distillation and fractionation products of tars and oils are the exhaust fumes of gasoline motors and Diesel engines. In line with the parallelism between the recent marked increase in automobile traffic and the increase of lung cancers, the existence of a causal correlation between these two phenomena has been postulated by several investigators (Lorentz; Heilmann; Duguid; Ferenszy and

Matolcsy; and others). This contention has been attacked on various grounds. Bloch and Widmer pointed out that the exhaust fumes of gasoline engines contain little or no carcinogenic ingredients as long as complete combustion of the fuel takes place. The absence of aromatic hydrocarbons in the exhaust fumes of gasoline motors was mentioned by Probst, who added that the degradation products of lubricating oil, which may be contained in the exhaust fumes, are also different from those of tar and are of non-aromatic character, according to the investigations conducted by Schlapfer.

Serious doubt of the correctness of this assertion was advanced also on statistical grounds. Assuming that the claims made were justified, Lehmann contended that there should be an excessive incidence of lung cancer among automobile drivers, garage workers and mechanics, and persons similarly employed. However, it was shown that members of such occupations were not affected more frequently with pulmonary malignancy than the general population (Passey and Holmes; Probst; Katz). Lehmann argued that a causal dependence between automobile traffic and the incidence of pulmonary malignancy should show a certain numerical correlation to the ratio of automobiles and the number of inhabitants in different countries (Germany: one automobile per 150 inhabitants; United States: one automobile per 5 inhabitants). The data available, however, indicate that lung cancers are not more frequent in the United States than in Germany, thereby providing an additional point against the conception of an etiological interrelation between automobile traffic, inhalation of exhaust fumes and incidence of lung cancer. It may be mentioned also that lung cancers increased in Riga and its environment before there was an appreciable rise in automobile traffic (Konrad and Franck; similar observation made by Syrek of Poland), while such a development in the number of automobiles used was not until recently accompanied in France by a rise in lung tumors. The available evidence does not support the theory advanced.

It may be mentioned briefly that Nikoloff reported a case of pulmonary carcinoma allegedly caused by the inhalation of benzene vapors. In commenting on this claim, Koelsch stated that benzene and its homologues do not exert specific carcinogenic effect upon the lung tissues. The presence of precancerous basal cell proliferations associated with chronic pneumonia were observed, on the other hand, by Brandt in mice exposed to the inhalation of vapors of tar distillates, xylol, and toluol.

Occupational Atmospheric Soot. There exist several casuistic observations of an occupational exposure to soot or tar which lend support to the contention of a pulmonary soot hazard. The occurrence of a carcinoma of the lung in a blacksmith, employed in a tar factory, was mentioned by Koelsch, who observed also a cancer of this organ in a tar worker 48 years of age exposed to tar fumes for 24 years. In a report appearing in the *Lancet,* reference was made to the presence of a lung cancer in a worker employed in a gas plant.

The occurrence of a pulmonary carcinoma in a worker, who had been employed for 20 years in an aniline plant and subsequently for 8 years in a briquette factory, was recorded by Rodenacker. Müllschitzky noted that during the last ten years only one case of pulmonary malignancy in a tar worker in Germany was recorded. The investigator added a new case of this neoplasia occurring in a man who had a scrotal cancer 15 years previously, a penile cancer 12 years previously, and multiple papillomas and epitheliomas of the skin 3 years previously.

While isolated case reports, concerning the appearance of lung cancer in different occupations having contact with tar, do not carry convincing weight because of their singularity, the observation of an excessive incidence of these tumors among a well defined group of workers with exposure to tar is of much greater significance in regard to the causal relationship. This type of evidence has been supplied recently by Japanese investigators (Kawahata; Kuroda and Kawahata). There occurred within 6 years, 21 cases of lung cancer among the workers employed in the generator gas plants of several steel factories. These men were exposed to the massive inhalation of fumes charged with fine, hot tar particles and high temperature distillation products of tar when they opened the holes on top of the generators for the frequent addition of coal and during the stoking process. The general incidence of lung tumors was 5 cases per 1,000 workers employed. There were 2 cases in 1933, 4 cases in 1934, 6 cases in 1935, 5 cases in 1936 and 4 cases in 1937.

The age distribution was as follows:

Years	35	38	39	40	42	44	45	46	47	48	50	54	65
Cases	2	2	1	2	2	2	3	1	1	2	1	1	1

The average age in this type of tar cancer of the lung is markedly younger than that of the cryptogenetic variety. The exposure time varied from 9.25 years to 23.25 years, the average being 16.6 years. In the oldest individual, the first symptoms developed 10 years after cessation of occupational contact. The right lung was involved in 12 cases, the left in 5 cases and a bilateral location existed in 9 cases. In 19 instances, the cancer was locally related to a large bronchus, in 8 cases, there was an intralobular location; while in one case a multiple, miliary variety was seen, which resembled grossly in appearance a miliary pulmonary tuberculosis. The histological examination of 5 cases showed 3 squamous cell carcinomas without cornifications and 2 adenocarcinomas. Several causal factors (a massive exposure to a highly carcinogenic agent; the high temperature of the inhaled material; the general irritative action of the dust and fumes inhaled) apparently combined to elicit not only a carcinogenic pulmonary response at a relatively early age, but also in a high proportion a bilateral involvement.

These claims and observations supporting a causative relationship between the occupational soot evil and lung cancer have met with objections from

various sources. Kennaway pointed out that there had been a pollution of air with soot for a long time before the increase in the incidence of pulmonary malignancy was noted. The rarity of this type of neoplasm among chimney sweeps (one case among 65 cases of chimney sweep cancer (1920-1923)) was cited by Kennaway in confirmation of his contention. Fischer-Wasels mentioned that the tar and pitch workers who inhale considerable amounts of tar dust suffer rarely from lung cancer in spite of the fact that they develop cutaneous carcinomas from their occupational exposure to this carcinogenic agent. A similar statement was made by Barnewitz and Behring in regard to the low incidence of lung carcinoma among the pitch and tar workers in the Ruhr district.

Habitual Exposure to Tarry Substances. The tobacco smoking habit provides an additional source through which tarry substances of known carcinogenic quality may enter the respiratory system. It has been suggested by investigators that this rapidly spreading habit, especially in regard to cigarettes, may have some relation to the increase and production of pulmonary malignancy (Bogen and Loomis; Schürch and Winterstein; Hruby and Sweany; Roffo; McNally; Lickint; Brockbank; Müller; and others).

It is contended that not only persons who smoke, but also those who inhale tobacco smoke because of environmental reasons over prolonged periods (waiters, housewives, etc.) show an excessive liability to lung carcinoma (Editorial, *J.A.M.A.*). The amount of tarry substances introduced into the respiratory tract by a heavy smoker is, in the opinion of Lehmann, much greater than that inhaled by an automobilist travelling on a tarred road. The occurrence of pulmonary malignancy in two heavy smokers was reported by Campbell. Similar observations on a large series of lung cancers (96) were reported by Müller. Lickint asserted that carcinomas of organs which are situated in the so-called smoke-tract (lips, oral cavity, larynx, trachea, bronchi, lung) are found more frequently in smokers than in non-smokers. This investigator sees in the exposure to tobacco tar the reason for the numerical discrepancy in the incidence of lung cancer among the two sexes, and for the more rapid increase of this type of cancer among men than among women. It may be added that this argument is open to question, in view of the increase of this habit during the last two decades among the female sex. Jackson and Jackson presented in 1941 statistical data indicating a small but progressive yearly increase in the incidence of laryngeal cancer probably caused by smoking. The proportion of men to women with this lesion was 10:1, and 95 per cent of the men were smokers.

Occupational Atmospheric Mineral Oil. There exists also some evidence incriminating the respiratory contact with carcinogenic oils for the development of malignant tumors of the respiratory organs. A relatively high ratio of laryngeal cancer was found by Kennaway and Kennaway in mule-spinners, who, during their work, inhale a mist of a carcinogenic shale oil used

for the lubrication of the spindles. A rather unique case of multiple crude oil carcinoma was reported by Roesch, who observed in a paraffin worker, 72 years old, a basal cell carcinoma of the upper arm which appeared 17 years after he ceased to work in a paraffin plant, and in which he was employed previously for twelve years. At the autopsy, which was performed four years later, three carcinomas were noted: the basal cell carcinoma of the upper arm, an adenocarcinoma of the stomach and an anaplastic squamous cell carcinoma of the lung. It stands to reason that the same carcinogenic agent contained in the crude oil, expressed from the paraffin, was responsible for the development of the three histologically as well as topographically different cancers. The conception is supported by observations made by Southam in mule-spinners. Southam noted as an interesting feature which was seen occasionally that mule-spinners exposed occupationally to a spray of a carcinogenic lubricating oil developed not only cancers of the skin (chiefly affecting the scrotum), but also of the stomach and the lungs. It is evident that these workers inhaled and also swallowed some of the oil globules which the spinning machines threw into the air. It must be mentioned, on the other hand, that Scott did not observe a single case of pulmonary malignancy among shale oil workers.

In this connection attention may be called to a certain group of workers (printers) who are to some extent exposed to the inhalation of a mist of hot paraffin, which may contain carcinogenic crude oils, shale oils or bituminous coal oils. Printers use sprays of hot paraffin to hasten the drying of fresh print. Injurious effects from such procedures have not been observed in the United States where the printers' wax is made from ozokerite, a natural bitumen of wax-like character, occurring near petroleum springs and obtained from Utah or Poland. This raw product is freed from asphalt, rosin, petrolatum, turpentine and burgundy pitch before it is used in the printing industry. It may be added that pure paraffin introduced into the lung is apparently not carcinogenic, as the repeated and prolonged insufflation of therapeutic sprays containing menthol and paraffin oil into the trachea so far have never given rise to pulmonary tumors but have produced chronic inflammatory paraffin granulomas (paraffinomas) and pulmonary cirrhosis.

A total of 23 cases of paraffin oil granulomas with accompanying induration of the lung has been recorded. While the pulmonary lesions appear to be neoplastic in character upon roentgenological and gross anatomical examination, the histological study shows readily and unmistakably their inflammatory character. These pulmonary nodules are of practical significance for differential-diagnostic reasons on account of the increasing and uncontrolled use of preparations containing liquid petrolatum by lay people in the treatment of respiratory difficulties (Ikeda; Bodmer and Kallós; Ellinger; Jaffé; Zdansky and Ellinger; Meursing; Ball; Graef; Davis; Tchertkoff and Ornstein).

Experimental Production of Pulmonary Cancer. Numerous experimental

attempts have been made to demonstrate the alleged causal relation between the respiratory or cutaneous exposure to tar and tarry substances (soot, tobacco tar, exhaust fumes), and the development of pulmonary malignancy. These efforts were accompanied partly with success, partly followed by failure.

The potential role of soot in the causation of lung tumors was investigated by Seelig and Benignus in a series of experiments using white mice for test animals. Soot obtained by sweeping the flue of a hospital furnace, in which bituminous nut coal from Kentucky was burned, was employed as bedding material in the cages as a substitute for the sawdust and shavings usually used for this purpose. The soot contained an average of 11.5 per cent tarry matter in the volatile portion and 5 per cent in the total soot. The exposure of the mice to the inhalation of sooty dust was intensified by adding to the amount of dust produced by the normal activity of the mice the massive amounts stirred up by shaking the cages 2 to 3 times daily. The one hundred test mice and fifty control mice used in this experiment came from a genetically pure strain, which for a number of years had been found to be tumor resistant and especially without any spontaneous pulmonary neoplastic lesions. The mice were three months old at the beginning of the experiment. They were subjected to the treatment above described for a period of eight months. Twenty mice died during the first six months of the experimental period, 60 were dead after twelve months and the mice surviving for the longest time succumbed within eighteen months after the start of the experiment. The lungs, examined in serial sections, showed only one case of adenocarcinoma among the fifty mice composing the control group, while two mice of the experimental group revealed an advanced epithelial hyperplasia of the bronchial mucosa and eight mice had malignant pulmonary neoplasms.

In a second set of experiments, Seelig and Benignus employed one hundred mice of a strain with known resistance to pulmonary neoplasia. The bedding consisted of lamp black mixed with 10 per cent of a carcinogenic tar. After an exposure for ten months, the examination of the lungs of these mice was negative for neoplastic manifestations. There were only a few epithelial inflammatory metaplasias and proliferations present.

While Seelig and Benignus felt that the fourfold incidence of lung tumors in the animals of the test series over that of the control series in the first experiment was of significance, the negative results obtained in the second experiment made them less certain as to the correctness of this conclusion, as they pointed out that the histological differential diagnosis between neoplastic and inflammatory hyperplastic and metaplastic changes in the lungs of mice was often very difficult.

Equally negative were the investigations conducted by Schnurer and Haythorn, who exposed animals to the inhalation of smoke formed by the continuous combustion of bituminous coal extending over a period of 80 days. The last animals were killed at the end of one year after the dis-

continuation of the exposure to soot. While some of the lungs showed at histological study the changes characteristic of a chronic organizing pneumonia, none revealed any evidence of a neoplastic condition.

Atypical epithelial growth was observed by Ibuka in the lungs of rabbits fifteen to sixty-eight days following the implantation of blocks composed of a mixture of soot and paraffin. Similarly inconclusive results were obtained by Schmidtmann, who exposed rabbits to the inhalation of the soot contained in the exhaust gases of a Diesel engine for periods up to 385 hours. The rabbits, which died 185 to 480 days after the cessation of this treatment, showed at the histological examination of the lungs a nodular type of anthracosis with scar formation and distortion of the bronchi. The bronchial epithelium had grown in some places into the alveolar lumina. These changes were most advanced in those animals which survived for the longest time. The epithelial proliferations, however, were in no instance of a neoplastic type. Schmidtmann concluded that these growth manifestations were the result of a stimulus exerted by traces of the fuel oil mixed with the soot.

The exposure of mice to the inhalation of exhaust gases produced by a gasoline motor, which differ, however, fundamentally in chemical respects from those emitted by a Diesel engine, proved to be entirely negative regarding a causative influence upon the development of pulmonary neoplasms. Twenty-six mice exposed by Smith over a period of five months to the inhalation of the exhaust fumes delivered by a Ford engine remained free, with one exception, from pulmonary neoplasia. This incidence of pulmonary tumor formation is within the normal range and, therefore, etiologically insignificant. There was no significant increase in the number of lung tumors over those found among the controls in mice exposed for seven hours daily during five days of the week for the greater part of their lives by Campbell to the inhalation of exhaust gases produced by an internal combustion engine. The concentration used was comparable to that existing in traffic blocks and garages. These results were confirmed by observations made by Schmidtmann. Experimental investigations of the carcinogenic potentiality of the sooty matter deposited in the exhaust pipes of gasoline motors are still outstanding.

A definite decision as to the role soot and sooty material may play in the production of pulmonary malignancy is not possible in view of the partly controversial and inadequate experimental evidence available. It may be mentioned that the clinical evidence, supporting a causative relationship between the inhalation of soot and the production of pulmonary carcinoma, is more suggestive than that provided by experimentation. This discrepancy possibly may be attributed to the fact that the duration of exposure to soot used in the experiments was perhaps too short to elicit a neoplastic response in the lungs of mice and rabbits. It seems to be advisable to alter the fundamental experimental approach to this problem by using animals which have a much longer normal life span than mice so as to be able to lengthen considerably the time of exposure. There does not exist any definite and fixed

relation between the normal life span of a particular species and its carcinogenic reaction time. While there are species specific variations in the reaction time and type of different species to the effect of carcinogenic agents, these are evidently not dependent upon the normal life span of the particular species.

The effect of tar upon the development and incidence of pulmonary tumors was studied experimentally in various ways (inhalation; intratracheal insufflation; cutaneous application, entailing partial introduction by ingestion and inhalation in addition to direct percutaneous resorption; intravenous injection). Rabbits, guinea pigs, rats and mice exposed by Staufer for several months to the inhalation of road dust containing tar did not develop any lung cancer, but several of the mice, after two or three months of this treatment, showed skin tumors. Similar results were obtained by Barnewitz, who kept fifteen mice in cages filled with powdered pitch and peat. The cages were shaken twice daily. The animals thus inhaled and swallowed pitch dust to a similar degree as the workers employed in pitch cellars. While cutaneous tumor formation started with the development of warts after eight weeks of this exposure and resulted finally in an incidence of cutaneous carcinomatosis of 56 per cent of the animals, none showed any pulmonary tumors, in spite of the fact that the lungs contained brown pigmentary matter. Bonne kept 31 mice in cages containing a mixture of tar and gum acacia, which were shaken daily, without obtaining pulmonary neoplastic lesions.

The experiments of Campbell, on the other hand, were apparently more successful. This investigator exposed mice of a mixed strain possessing a fairly low susceptibility to spontaneous formation of pulmonary tumors to the inhalation of a road dust containing 1.6 to 2.8 per cent tar. Every hour a moderate cloud of this dust was produced two to five times daily for five days of the week over a period of one year. The mice were three months old at the start of the experiment. While the incidence of pulmonary neoplasms in the control group, consisting of animals of the same age, was 14 per cent, that of the experimental group was 74 per cent. Approximately three-fourths of the mice surviving for a sufficient period developed in addition skin cancers. Similar experiments conducted with rabbits and guinea pigs were negative for pulmonary neoplasia.

The intrabronchial introduction of tar, by an insufflation of this substance through a tracheotomy wound, was practised by Kimura in three rabbits and ten guinea pigs. One rabbit and three guinea pigs survived this procedure for an extended period. The lung of the rabbit, killed eighty days after this operation, contained an adenomatous area, while one of the guinea pigs, sacrificed 140 days later, showed multiple adenocarcinomas with bone formation of the lung. Bonne, who once injected intratracheally a powdered mixture of tar and gum acacia into 104 mice, did not observe, on the other hand, after one year any increase in the incidence of pulmonary tumors.

In contrast to these either negative or doubtful results obtained by the experimental inhalation or insufflation of tar, the cutaneous application of this substance had a definite and evidently undeniable effect upon the development and incidence of pulmonary neoplasia of mice and rats in the hands of several investigators (Murphy and Sturm; Möller; Bonne; Schabad; Lynch; Puccinelli; Koose). When a tar solution in benzene was painted on alternating sites of the skin of mice, three to four months old, Murphy and Sturm observed that after 36 of these applications, given within 83 days, twelve out of twenty surviving mice showed one to six months after the arrest of the treatment single or multiple tumors of the lung, while no pulmonary neoplasms were found in twenty-two control mice of the same stock and age. In a second experiment on forty mice similarly treated Murphy and Sturm found a lung tumor incidence of 78.3 per cent among 23 surviving mice (being 9 to 10 months old), while control animals, which were even one to six months older than the test animals, did not show any tumors. Similar observations were made by Schabad after painting the skin of mice with tar (control series with normal incidence of spontaneous pulmonary tumors: 3.5 per cent; experimental tarred group: 20.56 per cent). There was also an increase in the primary neoplastic multiplicity of the lung tumors in the tarred series (63.6 per cent in comparison to that present in the control series 37.5 per cent), thereby corroborating observations made by Lynch. The results obtained by Puccinelli on mice and rats following the repeated application of tar to alternative sites of the skin in order to prevent the development of skin tumors, confirmed those of the previously mentioned investigators. Rats painted cutaneously by Möller, at first three times weekly and later twice weekly, did not develop tumors of the skin, while hyperkeratoses, hypertrichoses and epithelial cysts were formed. Six of the 24 rats surviving the treatment for 56 to 435 days, however, showed malignant cornifying bronchiogenic squamous cell proliferations. These cancers were found in rats painted for more than 300 days. The first evidence of a carcinomatous transformation of the bronchial mucosa was represented by the development of folds and papillary excrescences, sometimes associated with metaplasia, in the bronchial mucosa. The effect of cutaneous tarring upon the incidence of pulmonary tumors is illustrated by the following compilation of Bonne:

Age in Months	Tarred Mice		Non-Tarred Mice	
	Number	Lung Tumors	Number	Lung Tumors
5– 6	11	0	5	0
7–12	216	14	54	0
13–18	63	19	66	7
19–23	10	7	21	5

The carcinogenic mechanism of tar applications in the production of pulmonary tumors is still uncertain. The tar may be resorbed through the skin and reach the lung by way of the lymphatics or blood vessels, and the volatile portions of it may be excreted through the lung; the dried tar on the skin is inhaled in the form of dust or its volatile portions inhaled in the form of vapors; the tar is licked off and enters the body through the digestive system and thus reaches the lung in its original or metabolized form. In addition to such direct action of the tar upon lung tissue, there remains the possibility of a general constitutional effect of a specific or nonspecific nature (activation of congenital predisposition; activation of a carcinogenic virus) (Murphy and Sturm; Möller; Lynch; Rous).

The intravenous introduction of tar was practised by Tedeschi, who injected seven rabbits with 2 to 3 drops of tar, twice weekly and found in the animals surviving up to 80 days a hyperplasia of atypical epithelium of the bronchi, which was considered as of precancerous character. The repeated intravenous injection of a solution of a carcinogenic tar in liquid paraffin oil (5:95) into 32 rabbits once a week by Simonds and Curtis caused in 13 rabbits, after two to nine weeks of treatment, the development of an epithelial hyperplasia and metaplasia of the bronchial mucosa. In addition there were vascular thromboses, necrotic foci and adenomatoid lesions as well as masses of metaplastic spindle-shaped and squamous epithelial cells in association with granulation tissue. The epithelial growth was atypical and infiltrative in character but had not given rise to metastatic deposits. Whereas the nuclear irregularity in these epithelial foci was considered to be too mild for a malignant growth, these changes were often multicentric and were regarded as strongly suggestive of malignancy. The epithelial proliferations of the bronchial mucosa observed by Nakano in five female rabbits, 37 to 159 days after they had been treated once a month with intravenous injections of tar dissolved in lanolin, were interpreted as true malignant tumors, in view of the fact that the occurrence of spontaneous carcinomas of the lung has not been noted in rabbits.

The injection of tar directly into the lung of rabbits, which survived this treatment for up to 90 days (Garschin and Pigalew), resulted in the production of bronchiectatic abscesses associated with solid proliferations of the epithelial lining infiltrating the surrounding tissue and filling the bronchial lumina. The epithelial cells were stratified in arrangement, atypical in character and possessed hyperchromatic nuclei. In some areas they were of transitional cell type or were cylindrical in shape, while garland-like formations of basal cells or adenomatoid structures occasionally occurred. These lesions were interpreted as carcinoma-like, atypical, regenerative, epithelial proliferations. The production of carcinomas of the pleural serosa by the intrapleural injection of tar into rabbits was reported by Uno.

Attempts also were made to demonstrate experimentally the carcinogenic

properties of tobacco tar, but in none of these studies were the organs of the respiratory tract used as the test tissue, as skin and alimentary tract served for this purpose (Roffo; Schürch and Winterstein; Bogen and Loomis; McNally; Lu-Fu-Hua; and others).

The effect of shale oils upon the incidence of pulmonary tumors in mice is similar to that produced by tar, according to the investigations of Schabad, who tested the action of four different types of shale oils. Mice painted with these oils showed an increase in the incidence and multiplicity of lung tumors over that observed in control animals. However, there did not exist any parallelism between the cutaneous carcinogenic potency of a particular oil and its corresponding effect upon the lungs. Similar observations concerning the increase of pulmonary tumors in mice following the cutaneous application of various lubricating oils were made by Twort and Lyth. These investigators tested the various fractions of a Borneo crude oil and found that the incidence of pulmonary neoplasms was somewhat higher with the more viscous fractions, but the relative degree of viscosity of a fraction was not related to its carcinogenicity for the skin. In recent experiments Kling, Samssonow and Héros were able to show that corresponding effects upon the pulmonary carcinogenesis of mice could be elicited by the cutaneous application of a light lubricating oil, which contained, according to spectrographic analysis, benzpyrene.

Attention has been called previously to the influence which certain carcinogenic hydrocarbons (1.2.5.6-dibenzanthracene, methylcholanthrene, etc.) exert upon the incidence, latency period or multiplicity of pulmonary neoplasms, in strains of mice varying in their genetic disposition to spontaneous pulmonary neoplasms, in connection with the discussion of the hereditary factors (Lynch; Andervont). While these observations were made on mice which had received the carcinogenic hydrocarbons by the cutaneous or subcutaneous method, thus leaving open the argument that the chemical might have acted in an indirect way, recently Andervont showed that the direct introduction of 1.2.5.6-dibenzanthracene into the lung of mice caused the development of pulmonary tumors.

While studying the question whether these exogenous carcinogens injected subcutaneously or intravenously act directly on the lung following their resorption from the site of injection or bring about a release of the inherited carcinogenic pulmonary tendencies by a systemic influence, Andervont concluded that the evidence available pointed to a local action of the exogenous carcinogen on the lung tissue. In support of this opinion Andervont listed the following observations: a) when silk threads coated with a carcinogen are placed into the lungs of mice, tumors develop around these threads, indicating the direct and local effect of these substances upon the lung tissue; b) the intravenous injection of dibenzanthracene absorbed on charcoal is followed by the appearance of tumors in the lung, where a part of the charcoal particles

are phagocytized; if, on the other hand, such a preparation is introduced subcutaneously, no pulmonary tumor formation results, because the carcinogen is evidently held back at the site of injection; c) the importance of the rate and amount of absorption of a carcinogen subcutaneously administered into the organism upon the incidence of lung tumors is demonstrated by the fact that the injection of serum dispersions of a carcinogen, which are readily absorbed, is followed by the development of a larger number of pulmonary neoplasms and a smaller number of subcutaneous tumors at the site of injection, than when the same carcinogen is introduced, dissolved in lard, from which it enters the organism at a slower rate; it is apparently for this reason that the intravenous introduction of a carcinogen (dibenzanthracene) is more effective in the production of pulmonary neoplasms than the subcutaneous treatment; d) the evident dependence of experimentally induced pulmonary neoplasia upon the presence of a sufficiently large amount of the carcinogen in the organism is shown by observations made by Lettinga, who found that the subcutaneous introduction of very small amounts of dibenzanthracene was followed by the development of tumors at the site of injection only, while the injection of large amounts of this carcinogen evoked the production of subcutaneous as well as pulmonary neoplasms, suggesting thereby that the excess of large amounts of a carcinogen locally deposited overflows into the organism and causes the development of tumors in a susceptible organ. The experiments conducted by Perry and Ginzton demonstrated that this pulmonary effect of 1.2.5.6-dibenzanthracene is not an organ specific and restricted one, as these investigators succeeded in eliciting through repeated application of 1.2.5.6-dibenzanthracene and theelin to the skin of mice, not only the formation of adenomas and carcinomas of the lung, but also of benign and malignant tumors of the skin, uterus, vagina, kidney, stomach, bladder and colon. These observations are a striking illustration of the fact that the chemical character of the carcinogen, the dose, the type and the site of its application evidently control to a large extent the site, organic distribution, organic and general multiplicity and the biological character of the neoplastic response observed in the particular case.

Experimental studies by Andervont have demonstrated that not only 1.2.5.6-dibenzanthracene and 20-methylcholanthrene, but also 2-amino-5-azotoluene and 3.4.5.6-dibenzcarbazole, when subcutaneously administered, are capable of eliciting pulmonary growths in mice, in addition to causing hepatomas and, in the case of the dibenzcarbazole, also subcutaneous sarcomas. The injection of sudan III, an azo-dye, dissolved in olive oil and sodium cholate into the pleural cavity of rabbits, caused a stratification, proliferation and swelling of the serosal epithelium with the formation of transitional and prickle cells, while the alveolar cells in the adjacent region assumed a cuboidal or columnar shape (Young). The observations indicate that a great variety

of chemical agents are capable, in the experimental animal at least, of influencing the occurrence, incidence, or biological character, of pulmonary neoplasia.

c. Physical Agents

Physical agents which have been incriminated in the production of occupational tumors of the respiratory system are either of a specific type (radiating energy, radioactive substances) or they are of nonspecific character (mechanical trauma).

I. PHYSICAL AGENTS OF DEFINED TYPE

a) Radioactive Substances; Lung Cancer of the Schneeberg Miners, Joachimsthal Miners and Workers in Radium Laboratories

Historical Aspects. The occupational cancer of the organs of the lower respiratory tract is one of the oldest occupational tumors known. These neoplasms affect mainly the workers employed in certain mines from which radioactive ores are recovered and which have been worked for many centuries. It is only very recently that isolated cases of this type of occupational tumor have been observed among chemists, technical assistants and workers engaged in the purification and commercial handling of radioactive substances.

The oldest known source of occupational pulmonary malignancy resulting from the exposure to radioactive ores is represented by the cobalt mines of the Schneeberg district in Saxony, Germany. The symptoms of this disease, prevalent among the miners of this region, were described by Theophrastus Bombastus von Hohenheim, called Paracelsus, who termed this ailment "mala metallorum" (1531). This disease of the miners of the Erzgebirge also was mentioned by Agricola (1521-1527 and 1546), Matthesius (1559), Pansa (1614), Engelschall (1725), Henckel (1729), Scheffler (1770) and Kuchenmeister (1869), who referred to it as "Bergkrankheit" (mountain sickness). The true nature of this fatal condition, however, was not recognized at that time and this miner's disease often was mistaken for tuberculosis of the lung (phthisis of the miners). It was not until 1879 that this occupational illness of the lungs was diagnosed properly as a malignant tumor (Härting and Hesse), but even then the correct histogenetic character was not determined until many years later (Schmorl 1926). Following the report of Härting and Hesse, an appreciable number of investigations have dealt with this important occupational disease (Cohnheim (1882); Aucke (1884); Arnstein (1913); Uhlig (1920); Risel (1921); Schmorl (1923); Beyreuther (1924); Rostoski, Saupe and Schmorl (1926); Weber (1926); Rostoski (1928); Schmorl (1928); Rostoski and Saupe (1930); Schmidtmann (1930); Lange (1935); Neitzel (1935); Döhnert (1938)).

Among the miners, working in the uranium mines of Joachimsthal, located on the southern slope of the Erzgebirge, in the Sudetenland, it had been

known for many years that a respiratory disease commonly occurred which was symptomatically similar to that observed in the Schneeberg district. These mines have been worked for several centuries. The knowledge of this similarity apparently induced Härting and Hesse in 1879 to inquire of the officials of the Joachimsthal mines, whether the occurrence of pulmonary malignancy among the miners of Joachimsthal had been observed. The answer received was negative. When this inquiry was repeated by Uhlig in 1920, the official answer still stated that no instances of pulmonary malignancy had been observed among the miners employed in the uranium mines at Joachimsthal. It was not until 1926 that Löwy reported from Prague the first two cases of pulmonary malignancy among the miners of Joachimsthal. An investigation started subsequently revealed that this condition was apparently as common among the Joachimsthal miners as it had been shown to be among the Schneeberg miners fifty years previously. From the evidence disclosed at that occasion, it became relatively certain that many miners had died from this disease during past centuries. Additional reports on the occurrence of lung cancer among the miners in Joachimsthal and the various aspects of this condition were published by Šickl (1928); Löwy (1929); Beutel (1931); Pirchan and Šickl (1932); Stocklasa (1933); Humphris (1934); Parade and Paschke (1934); Ziel (1935); Tschelnitz (1935); Governmental Commission of Czechoslovakia (1935).

The observations made in Joachimsthal had shown already that not only the miners of the uranium ores were victims of pulmonary malignancy, but that also some of the chemists and workers employed in the radium laboratories, where the ores were purified and processed for the isolation of the various radioactive products, were sufferers from this neoplasm. Reports of recent years (Neitzel (1935); Teleky (1937); Baader (1937)) indicate that similar cases have been found among the employees of other laboratories engaged in the purification and commercial preparation and handling of radioactive substances.

It is remarkable that no information is available as to the existence of similar conditions among the miners of radioactive ores in the Belgian Congo at Katanga and at Great Bear Lake in northern Canada. An emphatic denial, as to the occurrence of pulmonary malignancy among the miners at Katanga as well as among the workers and technicians engaged in the purification of the African ores in the laboratories situated at Oolen (Belgium), was made by DeLaet in 1934. The presence of pulmonary malignancy among radium miners and workers also was not mentioned by Jacobs in his description of this plant operated by the Belgian concern. DeLaet even stressed the fact that the workers handling the ores were exposed to the inhalation of massive amounts of the dust. It may be possible that the statement of DeLaet in regard to the absence of lung cancer is correct, as the Belgian mines and laboratories have been in operation only for twelve years and in view of the

fact that the exposure time essential for the production of this disease seems to be not less than ten years (Martineck). It would be fallacious, however, to conclude from this negative observation upon a future immunity of the Belgian miners and workers as to the occurrence of pulmonary cancer (Maisin). The Canadian operations in radioactive ores are of too recent date to have yielded their share of occupational pulmonary malignancy. In case the Belgian and Canadian operations should be conducted without the essential and comprehensive protective measures for the workers, the prospects for an epidemic-like appearance of lung carcinomas among their employees can be anticipated in the not too distant future.

The Pulmonary Tumors at Schneeberg

Technological Notes. The mines in the Schneeberg district were opened in the year 1410 for mining ores containing silver, copper and iron. From the year 1470 on, these mines were also worked for the production of cobalt and arsenic containing ores. During the seventeenth century, the mining and smelting of cobalt ores were supplemented by the establishment of a cobalt dye industry (cobalt blue) in this region. During subsequent centuries, the ores also were used for the extraction of bismuth, nickel and uranium. In addition to these metals, they contain small amounts of tin, zinc, lead, magnesium and manganese (Rostoski). More recent investigations have shown that the water and the air of these mines are radioactive. The basic rock contains silicates (granite). Bismuth occurs in a metallic form, while cobalt and nickel are found as arsenides (up to 0.45 per cent arsenic is present in cobalt ore). There are eight mines in the Schneeberg region. The mine shafts extend to a depth of 1,500 yards (Brockbank).

The number of miners employed in these mines has varied a great deal during the centuries, depending mainly upon the types of ores for which these mines were worked. There was usually a decrease in the number of workers following the exhaustion of certain ores (silver and copper), while an increase occurred whenever the ores yielded metals heretofore not utilized. The mining operations at times gave work to 700 or 800 miners. Their number gradually was reduced after the turn of the century as the operations were curtailed for competitive reasons. This development was accentuated after the World War, so that there were only 149 active miners in 1921 and still less (54) in 1926 (Rostoski). However, the mines were reopened in 1933 and the mining operations are carried on in recent years on a much more extensive scale (Baader). Hueck stated in 1939 that there are 70 miners employed in the Schneeberg mines.

Exposure. The operations in the mines always entailed the production of a certain amount of dust. This hazard has been aggravated considerably since the introduction of dynamiting and the use of air-pressure tools to drill holes into which dynamite sticks are placed. The dust of the rocks contains particu-

larly silicates, arsenic and cobalt. In addition there is in recent decades an exposure to powder fumes. As the mines contain much water, the wooden supports rot readily and are covered by a fungus growth which may be transferred to miners handling food with soiled hands. It is also maintained that some of these fungi give rise to the production of the gaseous diethyl arsine which is inhaled by the workers. A second gaseous hazard of much importance is the presence of appreciable amounts of radium emanation in the rock, water and air of the mines.

While masks, respirators, mouth sponges, etc. were tried to prevent the inhalation of dust, these appliances were little used by the miners. The dust, fume and gas hazards present in the mines were aggravated by the existence of insufficient ventilation. Only in relatively recent years has an appreciable improvement in these conditions occurred through the replacement of the dry drilling technique by wet drilling methods and through the introduction of a more efficient ventilation system. In former times the miners were subjected not only to defective sanitary conditions but also to excessive physical labor in the mines (Uhlig). The mine shafts have been equipped in rather late years with lifts to facilitate the access to and exit from the mines. In former years the miners had to climb long series of ladders for this purpose.

Apart from these occupational factors, there existed certain environmental conditions which entered into the etiological considerations mentioned by various investigators at different times concerning the causation of the lung tumors. It was pointed out that the miners and their families had lived for many decades under bad economic conditions reflected by deficient housing and nutrition, and that they had acquired thereby a general weakening of their normal constitutional resistance against the effects of exogenous occupational and environmental noxae. The miners were thus made susceptible to colds and inflammatory disorders of the lung.

Causative Mechanism. The various potentially causative factors listed have been studied as to their significance and relation in the development of pulmonary malignancy in the miners. The great majority of these factors has been eliminated from further consideration on the basis of the investigations made. Inherited as well as acquired constitutional factors of non-occupational origin could be dismissed without any great effort, when it was shown that only the miners were affected by the pulmonary disease, while the rest of the population of the region, including especially the family-members of the diseased miners did not develop lung cancers, even when they were suffering from chronic respiratory ailments. The examination of 176 workers employed in the cobalt blue plant, where the ores removed from the mines were crushed under the production of a considerable amount of dust (containing FeS_2,$CoAs_2$,$NiAs_2$, and silica) and then were used for the manufacture of the pigments, did not reveal evidence to support the conception that these workers were disposed in an appreciable degree to the development of pulmonary neo-

plasia (Baader; Rostoski and Saupe). Similarly negative observations were made of miners working in the nearby Johann Georgenstadt district. For these reasons a constitutional defectiveness of the population of the Erzgebirge does not play any contributory role in the production of the Schneeberg cancers, as claimed by Härting and Hesse; Rostoski, Saupe and Schmorl; and Lange.

Experimental investigations as well as clinical evidence do not support the contention that the flora present in the mines (fungi—penicillium, aspergillus—and bacteria) possesses specific carcinogenic qualities. Inasmuch as powder fumes, which were considered by Härting and Hesse as of possible causal significance, do not exhibit such an action upon workers exposed to them in different occupational endeavours, this factor does not deserve further consideration (Arnstein; Cohnheim; Rostoski and Saupe). The claim as to a specific carcinogenic property attributed to cobalt could not be confirmed through investigations conducted in 1925 by a special committee of the Labour Office of the League of Nations among the workers employed in cobalt mines in other parts of the world (Canada: Cobalt City; Congo: Katanga; Norway: Skuterud; France: Allemont; Czechoslovakia: Dobschina). In Cobalt City 398 miners employed for 5 to 20 years were examined without finding a single case of pulmonary malignancy. A similar result was obtained at the examination of the miners of Dobschina. The statement made by Kaufmann that the cobalt miners in India show an excessive incidence of lung cancer is evidently the result of incorrect information. The chemical examination of the lung of a miner in Schneeberg dying from lung cancer did not show the presence of cobalt (Beyreuther).

The presence of arsenic in the rock dust and in the mine air (as diethyl arsine produced by the metabolic activity of fungi) has given rise to the contention that this known carcinogenic chemical was involved in the production of the Schneeberg cancer (Risel; Weber; Schmorl). Risel thus asserted that the arsenical dust activated the mediastinal lymph nodes into the development of a lymphosarcoma or, rarely, of an endothelial carcinoma. In support of this claim attention was called to the fact that the Schneeberg miners frequently were affected by a dermatosis of the hands, which was attributed to an arsenical exposure.

A more thorough and comprehensive study of this aspect, however, reveals numerous data which are not in accord with such a conception. Inasmuch as the allegedly arsenical dermatosis may be caused by a variety of other irritative factors present in the mines, anyone of which alone may produce such a condition of the hands (exposure to water, mechanical trauma with bacterial infection, radium emanation), this evidence is of very doubtful value, as it permits an interpretation more plausible than that given. The production of arsenical dust and its inhalation by the miners have been reduced greatly by the introduction of better ventilation, by the method of wet drilling and by the wearing of masks by drillers, while the possible

formation of diethyl arsine has been diminished by the treatment of the wooden supports with carbolineum, thereby impairing the growth of moulds. The chemical examination of the hair and nails of the Schneeberg miners for the presence of arsenic was negative (Döhnert), thereby indicating that an appreciable and prolonged exposure to arsenicals does not exist. This investigator called attention to the fact that the cobalt ores in several mines in France and Norway contain up to 60 to 70 per cent of arsenic, while the miners are free from lung tumors. Arsenic is also a constant component of coal (Belgium), but coal miners are not especially affected by pulmonary neoplasia. If, therefore, arsenic plays a causal role at all in the production of the Schneeberg cancers, it is only in a minor contributory capacity.

The inhalation of siliceous dust by the miners also has prominently figured in attempts to explain the occurrence of these cancers. Härting and Hesse thought that the chronic irritation of the mediastinal lymph nodes by the dust inhaled and deposited in them was the cause of an excessive proliferative activity resulting in the formation of lymphosarcomatous neoplasms. Following the establishment of the epithelial nature of the Schneeberg tumors, Schmorl asserted that the rock dust deposited in the peribronchial lymph nodes and lymphatics caused the production of small mucosal bronchial necroses and ulcerations which finally led to a malignant transformation in the bronchial epithelium. Upon a more careful and extensive analysis of the cases of Schneeberg cancer, it was observed, however, that these tumors occurred in lungs showing little or at least no unusual degree of pneumoconiosis. There did not exist any parallelism between the degree of pneumoconiosis and the incidence of pulmonary malignancy among the Schneeberg miners. Inasmuch as such causal interrelations cannot be demonstrated for silicosis and pulmonary cancer in general, it is highly improbable that they should be present in this particular instance. There remains, however, a possibility that the chronic inflammatory changes set up in the lungs of the miners by the pneumoconiotic process may create a susceptible soil or produce a certain proliferative sensitivity of the pulmonary tissue for a more ready neoplastic response to the exposure to the radium emanation present in the rocks, water and air of the mines and inhaled by the miners.

This actinic factor in recent years has gained increasingly in importance and the evidence available at present supports the conception that it is the chief cause of the Schneeberg cancers. It is remarkable that the first suggestion as to the possibility of an actinic etiology (radium and radium emanation) of these tumors came from a layman employed in the office of the mines (Uhlig). The possible role of an exposure to radioactive uranium ores was again maintained in 1913 by Risel. However, this suggestion was not received favorably at that time, in view of the fact that nothing was known in regard to the existence of similar conditions among the miners in Joachimsthal. After Uhlig had commented favorably on the possibility of a causal significance of

radioactive substances, more extensive and thorough studies of the radioactive conditions prevailing within the mines and in the surrounding regions were made.

The first measurements of the radioactivity of the air in the Schneeberg mines were made by Ludewig and Lorenser, who found a maximal content of 50 Mache units per liter (1924). Investigations made by Neitzel, during the years 1923-1934 in these mines, brought out the fact that there were marked variations in regard to the degree of radioactivity in different parts of the mines. The air at the site of the drill holes contained 36 to 46.5 Mache units per liter, while the air at the bottom of the mine shaft had only a content of 2.6 to 11.7 Mache units. The water dripping from the walls of the mine ducts had a radioactivity ranging from 5.5 to 221 Mache units per liter, depending upon the location and originating from dissolved radium element (3.44×10^{-4}MC per liter of water). Assuming that the air in mines contains an average of 40 Mache units per liter and that a Schneeberg miner works seven hours daily and 300 days per year, Lange calculated that such a person would receive a yearly dose of 12.4 mg. of the radium element.

In recent investigations of Rajewsky concerning the emanation content of the air in the mines, it was found that the concentration varied in different localities between 0.02 and 183 Mache units per liter. It was significant that the mine which had the highest emanation content was known among the miners as the "Todesschacht" (death mine). The emanation content in the mines was in general between 6 and 8 Mache units. Rajewsky added that the emanation content of the mine air was, especially in former years, above the non-toxic level, and thus may have caused injury, representing at least one of the factors operative in the causation of Schneeberg cancer. While studying the urine of two hewers, following several days of work in drilling operations in the mines, Neitzel found 21.2 to 29.4 Mache units of radium emanation per liter of urine. As these figures are rather high, he concluded that there exists a more marked exposure to radium emanation near the sites of drill holes than in other parts of the mines. This observation is of special significance, as pulmonary malignancy is particularly frequent among the miners employed as hewers, thereby supporting the conception of a radioactive origin of these tumors (Neitzel; Fischer-Wasels).

It may be mentioned in this connection that radioactive rock formations and waters in springs and brooks are found in a larger area of the Erzgebirge. The air in the mines of the Johann Georgenstadt district, which is situated in close proximity to the Schneeberg region contains, according to Rostoski and Saupe, 1.8 to 6.6 Mache units per liter, rarely up to 40 units, while a few Mache units are present in the water of these mines. In a more detailed survey of the radioactive water of the baths in Schlema it was shown that the water contains 300 to 5,500 Mache units. Lange pointed out that the attendants of these bathing establishments should be exposed to the inhalation of an appre-

ciable quantity of radiation. As no case of lung cancer has been observed among them so far, Lange suggested that either better sanitary conditions and more effective ventilation had reduced the actual degree of exposure or that the duration of contact with the radiating energy has been too short for the production of a neoplastic response.

The radioactive rock formations of these parts of the Erzgebirge are turmaline granite, containing 4.57×10^{-12} gm. radium per gram of granite, phyllites and glimmer shale, which are less active than the granite. The radio-active mines of Joachimsthal, Wittigsthal, Schneeberg and Oberschlema are located in the phyllite district. The water of the entire region is radioactive. Many springs contain 50 Mache units per liter of water. In Oberschlema, where the water is very rich in radioactivity due to disintegration of pitch-blende contained in the rocks, the water may have up to 12,000 Mache units, or 1/4,000 mgm. of radium per liter. The average activity of the water of the creeks and river is much lower, however, ranging from 5 to12 Mache units. Radioactivity is also demonstrable in the soil, plants, animals and man living in these regions.

In following up his physical investigations Lange prepared a geological map of this region, marking the radioactive and non-radioactive districts. When he traced the local origin of the 266 proven cancer cases, observed in the surgical department of the local hospital (Aue), he found that the general cancer incidence of the radioactive regions to be three-fold that of the non-radioactive regions, which contained mainly phyllites and glimmer shale.

Experimental Investigations. The first experimental attempts to determine the cause of the Schneeberg tumors were made by Härting, who fed fungi to mice with a negative effect. The same result was obtained by Arnstein, who fed mud from the mines, together with cultures of fungi, to rats. Doubts were thrown upon the actual production of diethylarsine by the fungus growth in mines by the inconclusive outcome of the studies of Rostoski, Saupe and Schmorl, who used cultures of hyphomycetes in their experiments. The potential carcinogenic role of arsenic, in conjunction with an exposure to the dust from drill holes, was investigated by Schmidtmann, who used the dust obtained from six drill holes of different types of rocks at Schneeberg. Epithelial bronchial proliferations were seen in rats exposed for a period of two years to the inhalation of those two types of dust which contained the highest amount of arsenic. A similar result was obtained when rats were fed small amounts of arsenic in addition to being exposed to the inhalation of those types of dust which had been proven to be ineffective when acting alone. Inasmuch as the inhalation of street dust, in conjunction with arsenic feeding, did not cause any proliferation of the bronchial epithelium, Schmidtmann concluded that arsenic was neither the only nor an essential cause of the Schneeberg cancers. Similarly negative were experiments of Schmorl and Rostoski, who exposed mice to the inhalation of dust from drill holes and

of radium emanation. Schmorl tried, also unsuccessfully, to demonstrate a carcinogenic action of the dust from drill holes by rubbing this substance into the skin of rabbits.

The most recent attempt to reproduce the pulmonary cancer of the Schneeberg miners in experimental animals was made by Döhnert, who kept white mice in cages, for a period of 17 months, in the mines near the drill holes, so as to obtain a most severe exposure to the dust as well as to the radium emanation. Of the 48 mice in the experiment, 28 died from pulmonary infectious processes. While the organs of two mice were used for the study of radioactivity, the tissues of 26 mice were subjected to a histological examination. The mice showed, with increasing exposure, a desquamative bronchitis with regeneration of hyperchromatic, small, stratified, non-secretory epithelial cells forming papillary excrescences and involving especially the terminal bronchioli. The solid bud-like projections of the bronchiolar epithelium sometimes extended into the alveolar spaces, and caused emphysema and secretory retention. There was some interstitial lymphoid infiltration present and, in addition, a moderate degree of chalicosis. A cholesteatomatous formation was seen in the lung of one mouse. Papillary adenocarcinomas existed in the lungs of two additional mice. The examination of the other internal organs revealed the presence of small papillary cystadenomata in some of the thyroids, with degenerative changes and increased vascularity in others. In addition to the two pulmonary adenocarcinomas (7 per cent of the total number), there were two cases of sarcoma of the mediastinal lymph nodes with remote metastases in numerous organs, and three cases of hemangio-endotheliosis of the mediastinal and cervical nodes associated with adenomas of the thyroid gland. The animals used in these experiments were full grown, adult mice.

The incidence of pulmonary neoplasms in the series of Döhnert is so low that a causal relation to the carcinogenic factors present in the mines can be almost definitely excluded, not only because old animals were used, but also mice were used without a known genetic constitution as to the occurrence of spontaneous pulmonary neoplasms. It is apparent that this experimental evidence has not contributed definite information which concerns the causative agent or agents active in the production of the Schneeberg carcinomas.

Incidence. When Härting and Hesse made their report in 1879 on the occurrence of pulmonary malignancy among the Schneeberg miners, approximately 650 miners were employed in these mines. Lung tumors caused the death of 150 miners in 1869-1877 (1869-1871: 63 fatalities; 1872-1874; 47 fatalities; 1875-1877: 40 fatalities). During the next two years (1878-1879), seventy-five per cent of all deaths among the miners were due to the same neoplastic condition (Arnstein). In a statistical analysis covering the deaths among the miners from 1879 to 1885, not including those among retired miners, Uhlig noted 72 fatalities from cancer of the lung. The diagnoses were made

by the company's physicians. The following compilation shows the distribution of these deaths based on the different years and age groups.

Number of Miners	Year	Age up to 25	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60 and over	Total
595	1879		2	4	2	1	3	2	1	1	16
663	1880			4	1		3	1		1	8
641	1881			1	2	1		3	2	2	9
634	1882	2		4	3		1	1	1	1	9
621	1883				1	1		1	3	3	8
633	1884		1	1	3	6	1		2		12
641	1885		1	1	1	2	2	1	2		10
		2	4	15	13	11	10	9	11	8	72

While, during the subsequent years, the incidence of pulmonary malignancy gradually decreased with the reduction of the number of miners employed, there were still 140 fatalities from this disease among the Schneeberg miners from 1879 to 1915. In the last two years of this period, only one case occurred in each year. A high degree of lung cancer morbidity and mortality seems to have existed, however, among the retired miners, as Arnstein stated that, during 1907 to 1911, one-third of these former miners who had been retired for incapacitation, had lung tumors, whereas 44 per cent of their fatalities were caused by this neoplastic condition.

The next investigation on the occurrence of pulmonary malignancy took place seven years later (1922), and covered the following 3 years and 6 months (Rostoski, Saupe and Schmorl). In a report published in 1926 these authors stated that, of 154 active and retired miners, 21 had died during this period. In thirteen cases, the autopsy showed the presence of a carcinoma of the lung, while of the 8 remaining cases, on whom a postmortem was not performed, two were strongly suspected of having also died from this condition, that is, 62 per cent and possibly even 71 per cent of all fatalities among the miners, were caused by a pulmonary malignancy. During 1926 to 1935, there was a total of 36 cases (Koelsch) of the Schneeberg disease. Hueck added, in 1939, 5 new cases which had occurred during the last three years and were found among 6 autopsies performed on miners in this period. The estimated total fatalities from lung carcinoma among the Schneeberg miners, for 1869 to 1939, are approximately four hundred. There seems to have occurred little change in the relative proportion of this cause of death to the total number of deaths. Three out of every four miners dying during these years were killed by neoplastic disease of the lungs (Weber (1926)).

An analysis of the number of deaths from lung cancer in relation to the number of miners employed and retired, indicates that the incidence during

recent years did not decrease but increased. The average yearly incidence in the period 1869 to 1877 was approximately 16 cases; there were approximately 10 cases a year during 1878 to 1885; 4 cases a year in 1879 to 1914; 5 cases a year from 1923 to 1925; and 3.6 cases a year between 1926 and 1935. Thus, while there was a reduction in the absolute number of cases of Schneeberg cancer in the last decade, the decrease in the number of active and retired miners was very much more marked, resulting in an actual increased incidence of the disease. During 1869 to 1877, when between 700 to 800 miners were employed, two miners out of every hundred died from lung cancer each year; during 1879 to 1885, with about 600 employed miners, 1.6 miners per 100 miners employed died each year from cancer of the lung; in 1921, when only 149 miners were working, about 4 miners died, or 2.6 miners out of 100 morkers employed. This actual increase in the incidence of pulmonary malignancy may be accounted for by the fact that the majority of miners at work in recent years were elderly men, who had been with the mines for many years, while new and young men were not added to the working crew due to the constantly shrinking operation of the mines. This conclusion is supported by Hueck's recent statement that 75 to 80 per cent of the miners die with lung cancer.

These data suggest, on the other hand, that the various technical and sanitary improvements introduced in the mines and for the miners have not yet yielded definite or appreciable reduction in the frequency of the disease. As at least ten to fifteen years must elapse before the efficacy of the precautionary and preventive measures that have been taken can be judged, as to the effect on miners newly employed after the introduction of such procedures, a considerable number of years may elapse before definite information on this matter may become available.

Age of the Miners at the Time of Death from Lung Cancer. The age distribution of the Schneeberg disease has undergone definite and marked changes since 1900. In more recent decades, the average age of miners dying from cancer of the lung was 55 years (range: 37 to 69 years—Rostoski, Saupe and Schmorl). These investigators noted that in former years the majority of miners died at an earlier age (between 40 to 50 years) from this disease. The correctness of this statement is born out by the statistical data supplied by Uhlig for deaths in 1879 to 1885. The age distribution of the 72 cases listed by this investigator is as follows:

Age up to	*25*	*25-29*	*30-34*	*35-39*	*40-44*	*45-49*	*50-54*	*55-59*	*60 and over*
Cases	2	4	15	13	11	10	9	11	8

Whereas the present age distribution of the Schneeberg cancers is similar to that of the cryptogenetic pulmonary carcinomas, the age distribution of the Schneeberg disease, from 1879 to 1885 was shifted toward the younger age groups (72.22 per cent of the cases occurred in miners under 50 years, in

contrast to 42.22 per cent in the cryptogenetic series). The cause of the shift into older age groups during recent decades is, at least in part, due to employing a greater proportion of elderly men in these times. The shift perhaps may also reflect a certain effect of the precautionary measures taken since 1880, resulting in a delay of the manifestation period of the tumors because of a reduced degree of exposure of the miners to the etiological agent.

Time of Exposure. The period of exposure necessary to elicit a neoplastic pulmonary response is not known definitely. The great majority of miners had been employed in the mines for periods ranging from 20 to 50 years before a pulmonary malignancy became manifest (Härting and Hesse). A shorter exposure time, however, was noted by Rostoski, Saupe and Schmorl, who found that tumors appeared after a period of 7 to 20 years. Koelsch, who noted that pulmonary tumors in the Schneeberg miners usually do not become manifest before less than 10 years exposure, unless a miner had been employed at an especially hazardous task accounting for an earlier appearance of the pulmonary cancer, made a similar statement.

A delayed development many years after the cessation of the occupational exposure is not uncommon (Uhlig; Risel; Schmorl; Arnstein) among incapacitated miners who have been retired because of nonspecific respiratory symptoms or for other reasons. Such a delayed appearance of the Schneeberg cancer was observed by Schmorl in four former miners, ten to eighteen years after their retirement.

Type of Worker Affected. Drillers and hewers are the most frequently affected class of miners, as they work under conditions which favor an exposure to a high concentration of radium emanation and rock dust in the presence of an imperfectly developed ventilation where they work. These underground workers come into first contact with newly opened sources of radium emanation released from rocks and water. They are exposed, therefore, most severely to the agent suspected to be the cause of the Schneeberg cancer. Carpenters, crushers, and similar types of miners are less often affected.

Heredity. The family history of miners suffering from pulmonary cancer often shows that brothers, fathers or other blood relatives, formerly working in the mines, succumbed while still young to the same disease. Such data, however, are in no way to be considered as evidence of an inherited susceptibility to pulmonary carcinoma, as this neoplastic disorder mainly attacks those who work under ground, while often sparing relatives who remain above ground. The occupational exposure sustained by miners, while working in the mines, is the exclusive causative factor which determines the development of a lung tumor. While the fact remains that the male members of successive generations of the same family, when working as miners, have suffered death from pulmonary malignancy characteristic of this occupation, it scarcely can be assumed that 70 to 75 per cent of the male population of this region should possess a hereditary predisposition to pulmonary neoplasia, which is

activated by the exposure to a highly unusual carcinogenic agent present in the mines. The environmental nature of the causative agent is indicated, on the other hand, by the fact that Hueck found 12 lung cancers in 14 autopsies performed on inhabitants of Schneeberg and vicinity.

Symptomatology. The first subjective symptom, indicating the development of a pulmonary tumor in these miners, is a protracted cough. This is slight and dry in the beginning, but gradually becomes more severe and complicated by a viscous, mucoid sputum difficult to produce. Occasionally, the expectorated matter may be tinged with blood. This persistent bronchitis may continue without further appreciable changes for years. In some instances an increasing degree of dyspnea develops, combined with dull pain in the chest and back. The general status may remain relatively good for many years until finally it gradually, or upon occasion, suddenly and rapidly takes a turn for the worse. Whenever this aggravation occurs, the dyspnea becomes increasingly severe and torturing. Coughing and expectoration then are more frequent and abundant. The sputum, however, rarely shows the raspberry-jelly-like character, considered typical of pulmonary cancer. The color of the skin becomes pale and greyish, or sometimes cyanotic with the progressive course of the neoplastic process. Larger hemorrhages from the lung occur; the swallowing may become difficult and the veins of the neck may become dilated because of the intrathoracic neoplastic masses pressing upon the esophagus and upon the blood vessels. Finally death results after the patient has become highly cachectic.

The findings obtained from a physical examination depend to a great deal upon the extent and site of the neoplastic process, and the simultaneous presence and the degree of complicating conditions, such as pneumoconiosis, which relatively often coexists with a carcinoma in the lung of the Schneeberg miners. The diagnosis of an early and centrally located pulmonary malignancy is made especially difficult in silicosis. The findings by Rostoski, Saupe and Schmorl considered most indicative of a pulmonary tumor are an intense dullness in the upper parts of the lungs, with markedly decreased or entirely absent breath sounds, and the absence of fremitus. The supraclavicular and supraspinal fossae are usually normal. A serous pleurisy may exist, but this is never of the hemorrhagic type. The physical findings do not differ essentially from those in a pulmonary cancer of unknown origin.

The examination of the blood reveals sometimes a marked leucocytosis (14,100; 23,800, and 36,400 leucocytes, respectively, in three cases observed by Rostoski, Saupe and Schmorl), while others reveal a leukopenia or a relative lymphocytosis. In three cases, there existed an eosinophilia of the blood (5; 6.25; and 10 per cent) and occasionally of the pleural exudate.

The examination of the chest with roentgen-rays often shows a picture which is, to a certain extent, characteristic of the Schneeberg type of lung carcinoma, that is, a combination of neoplastic and silicotic lesions of the lung.

It is obvious that the frequent, although not constant coexistence of these two conditions, interferes with the reliable diagnostic interpretation of roentgenograms. The silicotic processes produce spotty shadows with unsharp delineation and irregular outlines located in the region of the hilum, while the neoplastic involvement of lymph nodes of the hilum are characterized by sharply defined, round shadows. The primary intra-pulmonary lesion sometimes may be too small to be demonstrable in roentgenograms, or it may be obliterated by superimposed silicotic changes. In some instances the interpretation of roentgenograms is further complicated by the presence of a pulmonary tuberculosis.

The course of the Schneeberg cancer is slow, in general, as two to three years may elapse between the first definitely neoplastic manifestations and the death of the miner. This slow course is attributed by Rostoski to the impairment of the spread of the tumor cells in the lung and into the lymphatics by the coexistence of the silicotic fibrosing and obliterative lymphatic processes.

Pathology. The true nature of these occupational neoplasms has remained a matter of vague speculation or incorrect interpretation for a long time. Until Härting and Hesse recognized their blastomatous character, these pulmonary lesions were thought to be the result of some specific (tuberculous), or nonspecific inflammatory process (caused by the inhalation of dust). Even when the neoplastic nature of the disease had been established beyond any doubt, the correct histological diagnosis was missed entirely and remained a matter of dispute for many years afterwards. Härting and Hesse believed that they were dealing with a lymphosarcomatous condition starting from the mediastinal and hilum nodes and extending secondarily into the lung. This diagnosis was based on the fact that the neoplasms observed consisted mainly of small, round cells. A case studied by Aucke was interpreted as a "fibromatous lymphosarcoma". Several cases, examined by Weigert, were diagnosed as "endothelial carcinomas", which this investigator thought to be a rare variety of the lymphosarcomas. Even in 1921, Uhlig maintained that one of two cases investigated by him was a small round cellular lymphoid growth, probably of sarcomatous type.

Cohnheim, in 1882, who had seen sections of one case and had considered these to represent a carcinomatous growth, voiced the first doubt concerning the sarcomatous character of these neoplasms. Risel, reexamining one of Weigert's cases and two new cases of his own, confirmed the carcinomatous character of these pulmonary tumors, which were composed of a small type of cell. Subsequent investigators have corroborated this statement. When Schmorl in 1926 reported on a series of 21 Schneeberg cancers, their carcinomatous nature became definitely established. Schmorl pointed out that the diagnostic difficulties previously encountered were attributable to the fact that many of the carcinomas were of the small-cell type and that sometimes the histological

interpretation was complicated by the coexistence of a granulation tissue containing giant cells resembling those present in lymphogranulomatosis. The following histological types were represented in the series studied by Schmorl: 12 squamous cell carcinomas, of which 7 showed keratinization; 6 carcinomas simplex (polymorphous, indifferent epithelial cells); and 3 small, lymphoid celled carcinomas. In six cases, there were tumors of two different histological types present in the same lung. Primary multiplicity of lung cancers was found not infrequently (25 per cent). Schmorl considered primary multiplicity as characteristic for the Schneeberg carcinoma. It may be mentioned that in two cases there were, in addition to primary carcinomas of the lung, hypernephromas of the kidney present. Tuberculosis of the lung, unrelated to the neoplastic process, was found in six cases and pneumoconiosis was noted in 19 cases (moderate degree in 5 cases; marked degree in 14 cases).

Apparently, the neoplasms originate in the mucous membrane of the bronchi. Twelve were located in the left lung, and nine in the right one. Usually, the tumors were of firm consistency and white or yellowish in color. Metastases were always found in the bronchial and cervical lymph nodes. There were secondary deposits in the liver and kidneys in several cases. Bone metastases were found in only 5 out of 31 cases (Hueck). There is no reliable information available as to the occurrence of cerebral metastases, for usually the skull was not opened at autopsy. Whenever multiple primary tumors of different histological structure existed, they had formed separate metastases.

Medico-Legal and Sanitary Aspects. The Schneeberg cancer is recognized as a compensable occupational disease in Germany since 1926, following an official investigation conducted by Rostoski, Saupe and Schmorl during 1922 to 1925, a report on which was published in 1926.

The sanitary and technical conditions existing at the mines in Schneeberg have been improved greatly during recent decades. The inhalation of dust and radium emanation was reduced by the introduction of a more efficient ventilation system and the use of wet drilling methods. The growth of fungi was impeded by using lumber soaked in or painted with creosote. Lifts replaced the long ladders in the mine shafts. Working time was reduced considerably. The management of the mines, the physicians of the mining company, as well as private physicians in the surrounding communities, have become fully aware of the occupational hazard connected with the work in these mines. This knowledge must be reflected in a more efficient and thorough medical supervision of the miners. The data presented, however, indicate that an appreciable degree of occupational hazard is still existent and that the precautionary measures taken may be insufficient to provide that amount of protection to the miners which must be expected and insisted upon. In view of the fact that therapeutic procedures are entirely ineffective in combating the disease once it has become established, the only means of controlling

this fatal occupational disorder consists in the introduction of measures that will prevent occupational contact with the causative agent.

The Lung Cancer of the Joachimsthal Miners

Technological Notes. Joachimsthal, which is located on the southern slope of the Erzgebirge in the Sudentenland, has been the site of mining activities for several centuries. Silver mines were opened there in the year 1516. After the exhaustion of the silver ores, and toward the end of the sixteenth century, mining was continued on a reduced scale to recover nickel, cobalt, bismuth and arsenic ores. During the latter part of the last century, the mining activities in Joachimsthal were revived following the mining of uranium ores (pitchblende) used as the basic material for the manufacture of uranium pigments. These operations were greatly enhanced after the discovery of radium in pitchblende. Large quantities of uranium ores have to be mined for the recovery of radium as the uranium ores contain very small amounts of radium (3.4×10^{-7} gram of radium is in equilibrium with 1 gm. of uranium). A total of two grams of radium have been recovered in recent years from the uranium ores at Joachimsthal.

There were approximately 400 miners employed in the mines during 1929 (Löwy), while an additional 60 workers were engaged in the manufacture of radium and uranium dyes in factories and laboratories located in Joachimsthal. Invalids were estimated to number about 100. Somewhat lower figures were recorded by Šickl in 1931 (320 active and 80 retired miners). Hueck placed the number of miners at 250 to 300 in 1939.

Exposure. The production methods, used in the Joachimsthal mines, are similar to those employed at Schneeberg. The dust found in the mines contains crystalline slate, feldspar, quartz, sometimes calcium, lead, and occasionally arsenic, bismuth, nickel, cobalt and uranium. Běhounek has demonstrated that the dust is radioactive. The same property is exhibited by the air and the water of the mines. The radium emanation escapes through cracks in the rock (Běhounek). The statements made concerning the degree of radioactivity of the air vary to some extent. Pirchan and Šickl reported that one liter of air contains 4 to 15 Mache units, but that some parts of the mines might contain as many as 52 Mache units. An average of 10 Mache units and a range of 3 to 30 Mache units was recorded by Tschelnitz, while Neitzel noted a radioactivity of the air of 30 to 40 Mache units.

Causative Mechanism. There are evidently two agents which may possess etiological relations to the development of the pulmonary malignancies observed among men working in the Joachimsthal mines. The first factor is the dust, especially its siliceous component, and the second factor is the radioactive substance inhaled in the form of dust or gas. The dust hazard in the Joachimsthal mines is less pronounced than in the Schneeberg mines. The reason for this difference is not quite clear. It may be due to differences in the character

of ores, it may be connected with certain differences in mining methods employed, or it may have its cause in the use of respirators by the miners. Arguing from the erroneous conception that the pulmonary cancers appeared among the miners after the introduction of pneumatic drills, Humphris contended that these neoplasms were the result of the inhalation of dust containing silica particles and solid radium and were not due to an exposure to radium emanation.

This theory has received support by Tschelnitz, who believed that the chief cause of the pulmonary malignancy is represented by the inhaled silica particles, which, in his opinion, are so small that soluble quartz particles are given off that cause a chronic inflammatory reaction. This process is activated by the radioactive portion of the dust, leading ultimately to the development of a malignant tumor.

In the opinion of Tschelnitz the inhalation of radium emanation plays only a contributory role, the pneumoconiosis being of chief importance. The arguments of Tschelnitz are based on his calculations in regard to the amount of radioactive matter passing through and being deposited in the lungs. Tschelnitz estimated that during a seven hours' shift 5,000 to 10,000 liters of air containing 14,000 to 28,000 Mache units pass through the lungs of a miner, making a yearly exposure to approximately 7 million to 8 million Mache units. Assuming that about thirty grams of dust are inhaled yearly, and about 50 per cent of the dust is retained in the lung of a miner, an additional exposure to radioactive material from this source corresponds to an amount of radium equivalent to 1.5×10^{-8} gm. This estimate is too high, according to Běhounek, and, in his opinion, is in the neighborhood of 1.5×10^{-12} gm. Ra. per gram of dried lung. Inasmuch as Flinn has stated that the lowest amount of radium representing a hazard is equivalent to 1.5×10^{-6} Ra., Tschelnitz concluded that the quantities of radioactive matter passing or deposited in the lung were too small to exert a carcinogenic effect.

In support of his contention, this investigator pointed out that the rest period of 17 hours elapsing between two shifts was sufficient for the complete removal of any radon inhaled from the body, so that a permanent exposure did not exist. Tschelnitz based this argument on the observation of Meyer, who reported that radon inhaled is completely eliminated after seven hours. Inasmuch as Fernan and Smereka had shown that no short lived depots remain in the body when emanation-containing water is ingested and that long-lived degradation products of the radon are retained in only negligible quantities, Tschelnitz felt that his conception of the innocuousness of the exposure to radioactive matter by the miners was further strengthened by these observations. Reference was finally made by him to the fact that a patient, who took a drinking cure of radioactive water, received within 8 weeks 56 million Mache units without showing untoward effects upon the lungs, while a miner was exposed within a year to only 8 million Mache

units. There is, however, a significant difference between the two types of exposure, as the miner is subjected over a more prolonged period and for seven hours daily to a constant level of the radiation energy, while the therapeutic administration is relatively short lived and given in repeated large doses.

The negative attitude of Tschelnitz concerning the causal relation of the radioactive substances to the development of the pulmonary neoplasms in the Joachimsthal miners, however, was not shared by Parade and Paschke; v. Schnizer; Pirchan and Šickl; Löwy; and others. Inasmuch as a miner introduces, with the air inhaled during his work within ten years, between 4,200,000 to 8,400,000 Mache units (equivalent to 15.5 to 31 mgm. of radium) into his lungs, Stocklasa reasoned that the effect exerted by the radiating energy must be dependent upon the duration and the summation of the individual exposures. Stocklasa proposed that the cellular responses in the lung are the result of an injurious action of the gamma rays upon the cellular oxidases and peroxides and that these rays thereby may change the reaction of the lung tissue from a normal pH (6.2) to a markedly acid pH (3.6) because of an accumulation of lactic acid. The gamma rays thus would set in motion a cellular enzymatic metabolism in which the fermentative processes would predominate and which Warburg postulated to be the cause of a malignant transformation of normal cells.

An analysis of evidence available reveals definitely that the inhalation of dust is not an agent essential to produce pulmonary malignancy in Joachimsthal miners. The roentgenologic examination, as well as the postmortem studies of the lungs of diseased miners, have shown that there is either no pneumoconiosis present or only a slight to moderate one. It was, moreover, demonstrated that the ash of carcinomatous lungs, while containing silicon oxide, was not radioactive (Ziel; Tomicek). An important carcinogenic role of the dust is also made less likely by the fact that an appreciable proportion of the affected workers were not drillers and hewers, who are most exposed to the inhalation of dust, but carpenters and similar workers (Pirchan and Šickl). It was observed by the miners, on the other hand, that every discovery of a rich uranium vein was followed, after several years, by a markedly increased mortality among the miners, pointing strongly to the presence of a radiation factor.

The Joachimsthal lung cancer in all probability is not of recent date, that is, it did not appear following the introduction of the pneumatic drill. Many miners are said to have died at an early adult age exhibiting symptoms similar to those observed among the Schneeberg miners and incorrectly diagnosed as tuberculosis, as were those at Schneeberg. This contention is supported by the fact that after the correct recognition of the neoplastic character of many of the respiratory diseases prevalent among the Joachimsthal miners,

the formerly high mortality rate from tuberculosis dropped severely and its place was taken by pulmonary malignancy.

The evidence available points to the action of a causative agent which is eliminated rapidly after having done its destructive work in the body. Considering that all conditions as to the site, history, geological formation of the mines, and the type and duration of exposure of the workers are either very similar to or even identical in Joachimsthal with those existing in the Schneeberg district, and realizing that the most important and unique common factor in both mining activities is the presence of radioactive matter in the form of radon, it becomes increasingly certain that the causative agent, which elicits the neoplastic response in the lungs of the miners in both regions, is the radiating energy of radon inhaled. Attempts at an experimental reproduction of these neoplasms in animals so far have failed (Löwy).

Incidence. The first case of "radium disease" of neoplastic character was described by Löwy in 1926. The same author placed a second case on record in 1928, and reported three additional cases in the following year. During 1929 and 1930, there occurred 19 deaths among the miners and individuals formerly employed as miners (9). Autopsies were performed in 13 instances and cancer of the lung was found in 9 cases, while tuberculosis existed in two. These postmortem examinations were continued by Ziel during 1933 to 1934, as there were no autopsies performed during 1931 and 1932, due to the objections raised by the relatives of the deceased miners. After arrangements had been made by the government of Czechoslovakia concerning the payment of an indemnity to the relatives for the privilege of an autopsy, these studies were resumed in 1934. During 1934 and 1935, there were 15 necropsies with 4 carcinomas of the lung (30 per cent). The general incidence of death from lung cancer among the Joachimsthal miners was estimated by Šickl to amount to more than 50 per cent, while Hueck stated in 1939 that it was 47 per cent (against 75 to 80 per cent in Schneeberg).

In 1935 the Czechoslovakian government published an official report on lung tumors among the miners in Joachimsthal, basing its conclusions on the medical data obtained by the regular medical examinations (physical, laryngological, roentgenological) of the miners. In this official report it was contended that only 4 miners had died since 1932, and none had shown any evidence of pulmonary cancer at a postmortem examination. However, it was noted, that many of the workers suffered from hyperthyroidism and catarrhal complaints of the upper respiratory tract. These conditions were present in 90 per cent cent of the miners, yet none showed any evidence of even a preparatory condition suggesting the possible future development of a pulmonary malignancy. It may be stated that the information as to the incidence of lung tumors contained in this report is in stark contradiction of data reported from other sources. Moreover it may be added that the report appears to be unreliable, as

the occurrence of a malignant disease requiring an exposure time of considerably more than 10 years is not eradicated within 3 years by the mere installation of an improved ventilation system in the mines. This conclusion is supported by a recent communication of Peller, who analyzed data obtained from the former Czechoslovakian Ministry of Health for 1929 to 1938, and found that the mortality from cancer among the Joachimsthal miners of the age group 35 to 44 years and 45 to 54 years was enormously greater than that of the corresponding age groups of the population of Prague and Vienna (perhaps 20 times higher), while 90 per cent of all primary cancers found among the miners were intrathoracic. There were so far 19 cases of Joachimsthal lung cancer placed on record (Löwy; Pirchan and Šickl; Beutel; Ziel) between 1926 and 1935. It is not probable that this figure represents the actual mortality from lung cancer among the miners during this period.

Age. The average age at death from pulmonary malignancy is 49 years, according to Šickl (compared with 55 years in Schneeberg). The age distribution of eleven cases for which this information is available is as follows:

Years:	*36-40*	*41-45*	*46-50*	*51-55*	*56-60*	*61 and over*
Cases:	2	1	2	4	0	2

In a subsequent report it was stated that the average age of the miners with lung tumors was 53 years, that is, approximately the same as the age of death of the general population. This assertion stands, however, in peculiar contrast to information supplied by Neitzel on this subject. This investigator noted that the average age of 56 miners dying, during 1918 to 1928, was 42 years, while the average age at death for the general population in the Joachimsthal district during this period was 59 years. This information is in agreement with data contained in the history records of miners who died from lung cancer. In these documents it is stated that the male members of the family died not infrequently at an early adult age (between 30 and 42 years) from respiratory diseases. As the male members of the population of this region often have worked for many generations in the mines, this information has a significant circumstantial value.

Time of Exposure. The period of exposure, that is, the time of employment in the mines, ranged from 13 to 23 years. The distribution, according to the number of years exposed, is as follows:

Years:	*13*	*14*	*15*	*16*	*17*	*23*
Cases:	2	2	1	2	1	1

Type of Worker Affected. Of the affected workers eleven were employed underground (6 carpenters, 4 hewers and drillers, 1 mine foreman), while two worked above ground in the radium laboratories. Without an intimate knowledge of the conditions of exposure that prevailed in the mines for the

different types of workmen, it is not feasible to form an opinion as to the cause for the large number of carpenters affected with lung tumors. This occupational distribution, however, may not reflect differences in exposure for various types of workers, but may be an expression of the relative number of men employed in the different types of work being subjected to such a high amount of carcinogenic agent, so that minor differences in the degree of exposure between the various groups are effaced, as far as the biological neoplastic reaction is concerned.

Symptomatology. The symptomatology of the Joachimsthal radium disease is, in general, identical with that of the Schneeberg cancer. Tormenting and prolonged attacks of coughing, producing a small amount of tenacious, glassy sputum, are an early and suspicious symptom of pulmonary cancer. The sputum may contain many eosinophilic cells, but never tumor particles. The progressive cough becomes subsequently complicated by shortness of breath, stabbing pains in the chest and expectoration of a viscous, blood tinged sputum. The examination of the blood may show a radiation anemia and lymphocytosis, while a leucocytosis exists during an advanced stage. The general condition often remains good for a long time, but some cases show early loss of weight and emaciation. In cases with an unusually rapid course, the metastatic manifestations may occupy the foreground, while the subjective and objective symptoms of the lung may be much less conspicuous. Pleurisy is an uncommon complication. The roentgen examination of the chest may remain negative in some cases in the presence of definite subjective symptoms. The roentgenograms may show a single, sharply circumscribed, round or lobulated shadow or multiple densities. From the location of these shadows in the peripheral portions of the lung, Beutel concluded that the carcinomatous genesis in the peripheral bronchioli suggested a causative noxae which is inhaled.

The manifestation period varies greatly in individual cases and fluctuates between 10 weeks and 6 years. In five cases observed by Pirchan and Sickl, the disease terminated in death within less than a year with the formation of extensive metastases. These investigators concluded that the Joachimsthal tumors apparently are more malignant and cause a more rapid death than the tumors that occur at Schneeberg. It may be added that one of the cases reported by Löwy (chemist in the radium laboratory) developed, as the result of an occupational exposure to radioactive substances, not only a lung cancer, but also a leukemia.

Pathology. The right lung was involved in four cases and the left in five cases. According to their gross appearances, 6 cancers were circumscribed nodes; 1 involved an entire lobe; 1 was a mediastino-pulmonary mass; and 1 was a diffuse, peripheral, pleural form. Metastatic deposits usually were wide spread, indicating a distribution through both the lymph and blood channels (mediastinal, cervical, supraclavicular and periaortic lymph nodes;

bones, especially the vertebrae; pericardium; liver; spleen; brain; suprarenal). An atrophy of the testes existed in one worker employed in the radium laboratory (Neitzel). The histological examination of the neoplasms revealed an absence of adenocarcinoma which existed in the Schneeberg series. The following histological types were represented: squamous cell carcinoma with cornifications 1; squamous cell carcinoma without cornifications 1; small cellular or oat-shaped cell carcinoma 6; and polymorphous cell carcinoma 1. In one case of oat-shaped cellular carcinoma cysto-papillary structures were found, which were taken as indicating a probably pleural origin. Multiple primary tumors with different histological structure were observed in one case.

Medico-Legal and Sanitary Aspects. The radium disease of the Joachimsthal miners was recognized by the government of Czechoslovakia as a compensable occupational disease in 1932. It was made obligatory by special decree that the miners be subjected to a medical examination at two year intervals. It was stated at that time that a special law was being prepared which covered the enforcement and introduction of preventive technical measures in the mines and radium laboratories (technical and medical).

The ventilation of the mines was improved in recent years by forcing air into the mine pits. It was reported that in response to this measure the radioactivity of the air was reduced to an average of 2 Mache units. Since the Joachimsthal mines have come recently under the supervision of the German government, it may be hoped that the study of the fatal occupational neoplastic diseases occurring among the men employed in both the Joachimsthal and Schneeberg mines will be coordinated and thus may yield more quickly results as to the best methods for their prevention and diagnosis.

Lung Carcinoma Among Employees of Establishments Manufacturing Radioactive Substances

The evidence supporting an actinic origin of the lung carcinomas of the Schneeberg and Joachimsthal miners is highly suggestive, but not entirely conclusive, since the circumstantial clinico-statistical data in favor of such a conception are complicated by the presence of additional exogenous factors of doubtful causal significance (dust, arsenic, etc.) and the attempts at an experimental reproduction of these diseases have failed. Because of this uncertainty, it is of great importance that carcinomas of the lung of evidently occupational genesis have occurred among workers who are employed in laboratories engaged in the purification and production of radioactive substances, of their compounds and of various preparations and appliances containing radioactive matter to be used for commercial and medicinal purposes, as well as in technicians of therapeutic radium laboratories.

Incidence. During discussion of the Joachimsthal cancer mention was made of the occurrence of two cases of pulmonary malignancy among the workers employed in the laboratories of these mines, where the uranium ores are

treated for the recovery and purification of their radioactive components. One of these laboratory workers had been in contact with radioactive substances for a period of 25 years, while the second technical worker had an exposure of only nine years (Löwy), before they developed a pulmonary neoplasia. Similar observations were recently made in several commercial and therapeutic radium laboratories in Germany (Baader; Neitzel; Teleky).

In a plant in Berlin, in which commercial mesothorium containing 30 per cent of radium was handled, a woman with 20 years of occupational contact with this radioactive material developed a bronchial carcinoma located in the left lower lobe, which formed metastases in the hilum nodes, liver, ovaries and suprarenals. The pulmonary tissue examined by Rajewsky for radioactivity gave a positive reaction. The skin of the person showed, moreover, pigmentary disturbances indicating an injurious effect of the rays upon the skin. Two other technicians, employed in the same factory, succumbed to an extensive radiation fibrosis of the lung, while a fourth worker of this plant developed, in addition to a pulmonary fibrosis, a melanosarcoma of the skin. Another case of this pulmonary radium disease was mentioned by Teleky, who reported the occurrence of a pulmonary carcinoma in a female technician, employed in a radium laboratory, subsequent to the appearance of a radium necrosis of the upper jaw. Martland mentioned in 1939 that a carcinoma of the ethmoid cells had been observed in a girl who had applied luminous paint upon watch dials.

Occupational exposure to the inhalation of radioactive matter does not invariably lead to the development of a pulmonary malignancy, as was demonstrated by the presence of pulmonary fibrosis causing the death of two persons in a radium plant in Berlin. Additional cases of this type were published recently by Kalbfleisch; Tönges and Kalbfleisch; Doenecke; and Belt. One case was a chemist, 35 years old, with 2 years of exposure to radioactive material, while in the other report a female technician, 24 years of age, with 4 years of exposure was the victim. The histological examination of the lungs of these two cases did not reveal any lesions indicative even of a preparatory precancerous epithelial proliferation. The feature apparently common to all cases of pulmonary fibrosis of a radioactive genesis is the relatively short time of exposure in contrast to the much longer time seemingly necessary to elicit a neoplastic response in the lungs by the same agents.

The occupational radiation pneumonitis is comparable to the post-irradiative pulmonary fibrosis which is sometimes observed in patients who have been subjected to prolonged and massive roentgen-treatments for therapeutic reasons (malignancy of the breast or lung). The extensive induration of the lung may become the direct cause of death (Bauer; McIntosh and Spitz; Bauer and Schraer; Warren and Gates; Warren and Spencer).

Experimental Production of Pulmonary Pathology by Radioactive Substances and Roentgen-Rays. Several attempts were made to duplicate these

clinical observations experimentally. Granzow used for this purpose 89 female guinea pigs, which he irradiated with radium, the dose applied varying from 300 to 2,700 Ra El mgh. Apart from degenerative changes in the heart, muscle and liver, there were regressive lesions in the lung involving the respiratory and bronchial epithelium and the blood vessels. A small area of adenoid structure was discovered in the lung of only one guinea pig. This was located near a degenerated bronchiole and seemed to originate from the bronchiolar epithelium. While the structure of this adenoid proliferation carried a certain resemblance to an adenocarcinoma, Granzow was not prepared to state whether it represented a focus of a future malignant growth. Inasmuch as similar proliferative epithelial reactions occur not infrequently in the lungs of guinea pigs, as the result of nonspecific inflammatory conditions, the significance of this observation of Granzow as to a radioactive origin is extremely doubtful.

In an experimental approach to this problem several investigators used roentgen-rays. In 116 rabbits, whose chests had been exposed to various amounts of roentgen-rays, Engelstad found, in addition to acute inflammatory reactions in the lungs, sometimes associated in more advanced stages with the formation of fibrous connective and bony tissue, a bronchial epithelium with cellular monstrosities, stratification, giant cell formation, and metaplastic keratinization. In no case was there any evidence of a malignant epithelial transformation and proliferation. Similar experiments were carried out by Luedin and Werthemann, who irradiated the chest and the back of rabbits with roentgen-rays, using a dose of 500r at each exposure, and which was repeated in certain intervals from 10 to 43 times. The lungs of these animals were studied histologically 65 to 343 days following the cessation of this treatment. After the disappearance of a transient roentgen-pleuropneumonitis, receding several weeks after the beginning of the roentgen-treatments, a fibrosis of the lung tissue was noticed. Apart from inflammatory lesions, such as purulent bronchiolitis and bronchitis, bronchopneumonia, there were degenerative and regenerative proliferative changes present in the bronchiolar and alveolar cellular lining. The alveolar cells were swollen, vacuolated and desquamated. The bronchiolar epithelium showed an appreciable regenerative proliferative activity, forming solid epithelial strands of polymorphous cells invading occasionally the peribronchial tissue or extending into the alveolar spaces. These cells originated from the basal layer of the bronchiolar lining and consisted of spindle shaped or round cells containing atypical mitoses and pyknotic nuclei. While these hyperplastic processes were in some respects similar to carcinomatous lesions, Luedin and Werthemann doubted that they were of malignant character. In view of these negative results and contending that experimental evidence had shown that radioactive substances produced sarcomas exclusively, Uehlinger asserted recently that the Schnee-

berg and Joachimsthal lung cancers could not be attributed to the action of radioactive ores.

Medico-Legal and Sanitary Aspects. Although so far all attempts to demonstrate experimentally a carcinogenic action of radioactive substances upon the pulmonary tissue consistently have failed, the evidence of the statistical and clinical observations on hand does not leave any doubt that these agents represent the chief cause of the pulmonary malignancies observed in workers (miners, artisans, technicians, chemists, etc.) exposed to radioactive matter for occupational reasons. As these substances are used in varying degrees and for different purposes in practically every country, the pulmonary cancer caused by the prolonged exposure to radioactive agents should be placed on the list of compensable occupational diseases in all countries. Evans and Goodman stated recently that a prolonged exposure to air containing 100×10^{-11} curies of radon or thoron per liter may become the cause of neoplastic pulmonary lesions in man. These investigators recommended that a radon or thoron concentration at a level below 10^{-11} curies of these gases per liter of air should be maintained, so as to remain well within a safe range.

II. PHYSICAL AGENTS OF ILL-DEFINED TYPE

Mechanical Trauma. A direct trauma to the chest, resulting in a bruise of the pulmonary tissue, has been repeatedly related to or was observed in connection with neoplasms of the lung (Adler; Hölder; Curran; Lepine; Gillespie; Gomez; Georgi; Scott; and Forman; Barron; Schöpfer; Alnor; Hedinger; Weller; Wells and Cannon; Perutz; Kikuth; Graham; Fishberg; Luckow; Klotz; Fischer-Wasels; Pilgerstorfer; Fischer and Fenster; and others). In his monograph on carcinoma of the lung, Simons cited nineteen cases of traumatic carcinoma of the lung reported in the literature. The total number of cases of alleged traumatic origin, however, is by far too small to indicate that trauma of the chest is of any practical importance as a causative factor in the great majority of pulmonary malignancies. The significance of traumatic lung carcinomas is mainly one of medico-legal nature.

The trauma incriminated was not always one causing a laceration of the lung tissue. It was of such a type sometimes that only a molecular disturbance of an unknown character of the lung resulted. In many cases, however, the accidental injury to the chest produced the fracture of one or several ribs (Gomez; Wells and Cannon). The relationship existing between trauma and pulmonary tumor was obviously coincidental in many cases, that is, the accident to the chest called attention to the neoplastic process pre-existing in the chest by eliciting some acute manifestations. In Fischer-Wasel's case, for instance, a hemoptysis occurred 8 days after the accident, followed by a rapid aggravation of the neoplastic process, so that death ensued only three and a half months after the accident. The postmortem examination showed that the

tumor involved the left lower lobe, while the accidental injury affected the right side of the chest. Thus, the clinical symptoms and the rapid course of the disease, as well as the autopsy findings, demonstrated clearly that a causal relationship between the trauma and the pulmonary neoplasm did not exist.

A similar case was described by Fischer and Fenster, who reported the history of a patient developing swollen lymph nodes in the left supraclavicular, inguinal, and abdominal regions twenty days after having sustained a contusion of the upper left chest. A roentgen-examination, made at that time, revealed the presence of a well developed neoplasm situated in the left lower lobe. These investigators commented that the timely examination of the chest had not only removed diagnostic uncertainties, but had obviated any future medico-legal complications by showing convincingly that the advanced stage of the neoplasm existing so soon after the trauma excluded any causal connection between the two phenomena.

A frankly sceptical attitude toward the etiological relation between a chest trauma and a pulmonary malignancy is assumed by Ewing and concurred in by Knox. Wells and Cannon, on the other hand, are inclined to concede the occurrence of such interrelations in the exceptional case in which the circumstantial evidence seems to suggest the possibility and probability of a causal connection. This attitude is based on the following case observed by Wells and Cannon: A man, 50 years of age, was knocked down by an automobile and sustained a fracture of the third, fourth and fifth ribs on the left side in the region of the axillary line, associated with severe pain in the chest. The roentgen-examination, one day after the accident, did not reveal any other chest pathology, and especially no evidence appeared which indicated the presence of a pulmonary neoplasm. After an uneventful healing of the fractures, the patient developed a cough and a second roentgen-examination, made eleven months after the accident, showed the existence of a lung tumor in the left upper lobe. The postmortem examination revealed a small cellular carcinoma originating probably from the peripheral parts of the upper lobe, that part of the lung which had been exposed mainly to the traumatic effects. Wells and Cannon felt that the interval, which elapsed between the trauma and the discovery of the tumor, kept well within the rate of growth of these tumors and, furthermore, that the peripheral site of the neoplasm and the trauma agreed with its histological type. Their conclusion in this instance was that a traumatic etiology of lung cancer could neither be definitely proven nor disproven, but that the circumstantial evidence suggested an etiological relation between trauma and subsequent pulmonary cancer.

A counterpart to this relatively acute neoplastic response to a traumatic injury of the lung is represented by a case reported by Pilgerstorfer in which the interval between the trauma and the subsequent neoplastic manifestation extended to nine years. In this case a traumatic fracture of the ribs was followed by the development of a fibrous pleurisy in the affected region. Nine

years later a pulmonary neoplasm was observed in the region of the pleural thickening. The necropsy showed a tumor, located one cm. internally from the thickened pleura, originating from a smaller bronchus. While the long interval excludes definitely the pre-traumatic existence of the tumor, its nearness to the chronic traumatic residue makes a causal interrelation worthy of serious consideration.

In two instances gun-shot wounds through the chest, causing a laceration of the lungs, were followed by the development of a pulmonary malignancy (Gillespie; Luckow). In the case reported by Luckow a causal connection was denied by the compensation court, as the tumor developed fourteen years after the injury and remote from the scar tissue surrounding the splinter lodged in the lung. Cases with a delayed appearance of the lung cancer after a trauma raise the question of the occurrence of a traumatic scar cancer of this organ. For the medico-legal recognition of pulmonary tumors of this type, the same principles should be applied which have been developed for the evaluation of scar cancers in general. The occasional occurrence of primary sarcomas of the pleura and lung following a single trauma of the chest was mentioned by Lyssunkin, who cited the cases of Stern, Eckersdorf and Lewenstein in this connection. Trauma does not represent a main etiologic factor in the development of these sarcomas in the opinion of Lyssunkin.

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[V]

OCCUPATIONAL TUMORS OF THE UROGENOUS ORGANS

1. ANATOMICAL AND FUNCTIONAL ASPECTS

THE urogenous organs (kidney, renal pelvis, ureter, urinary bladder, urethra) fulfill various functions in a process by which metabolic waste products are eliminated from the body in the form of a watery solution (urine). The kidney has the task of urine production; the bladder functions as a collecting vessel for the urine; while the renal pelvis, ureter and urethra represent excretory passages through which urine passes to the outside. The anatomical location of these organs in the body, as well as their functional position at the end of a series of important metabolic processes, excludes the possibility of a primary contact of the urogenous tissues with any exogenous cancerigenic agents of occupational origin, such as exists with the cutaneous, respiratory and alimentary organs.

Extraneous agents, which may produce tumors in the various parts of the urogenous system, therefore, either must first penetrate or be absorbed by the cellular lining covering the outer surfaces, ducts and glands of the cutaneous, respiratory and alimentary system. After having thus entered the organism, these agents may establish contact with the cellular elements composing the urogenous organs either by way of the blood stream or by being in the urine excreted by the kidney. While it has been shown that the explanted mucosa of the bladder of the dog releases phosphatase (Huggins; Lucinesco and Cavalli; Neuhof; Abbott and Goodwin) and may secrete calcium and phosphorus (Entz), reliable evidence does not exist to support the assumption that other organic or inorganic exogenous or endogenous substances may be excreted through the transitional epithelial lining of the renal pelvis, ureter and bladder in man.

The occupational factors that give rise to the development of tumors in the urogenous organs are either chemicals, parasites or mechanical trauma.

2. CHEMICAL AGENTS—AROMATIC COMPOUNDS

The chemical substances which have been incriminated in the formation of tumors of the urogenous tract are products of coal distillation, that is, tar and its derivatives (aromatic amino- and nitro-compounds, coal tar dyes, paraffin, etc.). In view of the fact that the occurrence of tumors of the urinary bladder following the occupational exposure to chemicals was first observed in workers engaged in the manufacture of aniline dyes, these neoplasms were named "aniline tumors" of the bladder. This term, obviously, became a

misnomer, since it was shown later on that not only several other aromatic amines, but also related aromatic compounds, may exert a similar blastogenic action upon the urogenous organs. The terms "amido-tumors" or "nitro-tumors" were proposed by Oppenheimer in 1926 as more appropriate, but the name "aniline tumor" has remained the more generally used designation for tumors of the urogenous system caused by the occupational exposure to aromatic organic chemicals.

I. GEOGRAPHIC DISTRIBUTION AND INCIDENCE

"Aniline tumors" belong to that group of industrial neoplasms which have become more widespread during recent decades, following the development of coal-tar dye industries in countries in which such establishments were absent or of minor extent until lately. Therefore chemical occupational tumors of the urogenous organs, especially the urinary bladder, have been observed almost exclusively in countries possessing for some time large chemical plants.

The first industrial neoplasms of this type were reported in 1895 by Rehn in Germany, where the manufacture of coal tar dyes was started around 1860; Germany supplied before 1914 more than 80 per cent of the world production of aniline, its derivatives and related aromatic amines. More than 300 cases of aniline tumor of the bladder have been observed in Germany since that time (Baader; Rehn; Leichtenstern; Nassauer; Oppenheimer; Lewin; Bardenheuer; Bachfeld; Curschmann; Schwerin; Engel; Bauer (Th.); Brezina; Sebening; Seyberth; Sieben; Simon; Straus; Ullmann; Teutschlaender; Buettner; Arnstein; Posner).

The chemical plants located around Basel (Switzerland), which were established at about the same time as the German chemical factories, furnished the only other source of these neoplasms before World War I. The first cases from Switzerland were reported by Schedler in 1905. Their total number at the present time amounts to over 80 (Leuenberger; Mueller; Henschen; Barkmeyer). When, during and after the Great War, chemical factories were founded and developed to large scale production also in other parts of the world, aniline tumors soon made their appearance in other countries.

The first information as to the occurrence of bladder tumors in dye workers in England was offered in 1918 by Ross. This investigator stated that fourteen cases of villous growths had been observed, according to a report of the Chief Inspector of Factories, in a works where the men were engaged in handling aniline dyes made there. Young and Russell in 1926 noted that there was an excess of bladder tumors among workers of chemical factories and textile dyeing establishments in England. Bridge and Henry in 1928 stated that twelve fatal cases of bladder cancer had occurred among chemical workers since 1924. Three years later Henry, Kennaway and Kennaway recorded 61 fatalities of bladder cancer among chemical workers (dyers, dye

workers, dye mixers, workers in explosives and rubber, and other nonspecified chemical operations) in England and Wales during 1921 to 1928. Since that time approximately thirty new cases of bladder tumors among chemical workers have occurred in English plants up to the end of 1937 (Young and Russell; Henry, Kennaway and Kennaway; Bridge and Henry; Bridge; Wignall; Macalpine; Berenblum; Henry; Stallybrass).

Similar observations were made in the Union of Soviet Socialist Republics by Rosenbaum and Gottlieb in 1926 (3 cases) and by Abramyan, Romberg and Maynats in 1932; and in Austria by Scheele in 1926 and 1927 and by Schueller in 1932.

The first cases of aniline tumor in the United States were reported in 1934, i.e., sixteen years after the beginning of the production of synthetic dyes from aniline and aniline derivatives on a large scale. At that time Ferguson and his co-workers placed on record 25 cases, all originating in one chemical concern. The first of these cases was discovered in 1931 by Anderson. The number increased to 86 by the end of 1936, according to subsequent communications (Gehrmann; Wolfe; Evans; Washburn; Gay; Ferguson) and is, at the present time, approximately 100 cases.

A recent newcomer to this group of countries is Italy. While the occurrence of aniline tumors of the bladder was still unknown in Italy in 1934, according to Gaeta, who attributed this fact to the relative newness of the Italian chemical industry, di Maio reported 12 aniline tumors in 1936 and 1937 which had developed among 86 workers of a certain dye factory in the course of the last few years. An earlier Italian communication on this subject by Bianchi, in 1911, does not refer to Italian cases but describes cases observed in Germany (Carozzi).

In 1940 Japan joined the list of modern industrialized countries in which aniline tumors of the bladder have appeared. Nagayo and Kinosita mentioned three cases of papillomatous neoplasms of the bladder in workers of an aniline dye factory, of which one case ended fatally. There were, in addition, many cases of hematuria among men employed for more than 10 years in the following operations: naphthylamine, nitrobenzene, benzidine, etc.

The total number of approximately 550 occupational tumors so far are on record in various countries. It need scarcely be mentioned that this does not represent the total incidence, as numerous factors are at work to obviate accurate information. It may be pointed out, for example, that so far all such tumors observed occurred in male workers, in spite of the fact that during the late World War women were also employed in these hazardous operations in some German plants. While they were eliminated from these occupations soon after the end of the war, it is not likely that all of them escaped without subsequent formation of bladder tumors. It is more probable that, when these tumors occurred, their occupational origin was not recognized.

Also conducive to the reduction in number of aniline tumors correctly diagnosed is the usual unavoidable turnover of labor in chemical plants. Neoplasms of this type may develop many years after a workman has left a hazardous occupation. He may therefore forget about this occupation or may not mention it to his physician, as he does not appreciate the existence of a causative relation between work engaged in many years previously and his present ailment.

There is the distinct possibility that not all cases, recognized or suspected of having occupational origin, have been reported in scientific journals or governmental records. All the American cases, for instance, were observed in the plants of one chemical company. It is reasonable to think that similar conditions may exist in other chemical manufacturing concerns producing or handling the same or similar chemicals of the aromatic series. This contention is supported by a remark, made by Schwartz, in one of his papers on the industrial cutaneous hazards of organic chemicals. Schwartz stated upon this occasion that the workers of an American plant, engaged in the production of aromatic nitro-compounds (dinitrophenol), seemed to be affected by bladder tumors. Inasmuch as aniline tumors have occurred, according to published reports and on the basis of personal knowledge of this matter, only in operations handling aromatic amines, the information supplied by Schwartz must refer to an additional source of aniline tumors in the United States.

Similar conditions apparently have existed in former years in Germany. When Rehn, in 1905, reported the results of a general survey of German chemical plants where aromatic amines were manufactured or handled, he noted that tumors were recorded in only seven of the eighteen factories investigated, while in the remaining eleven which had been engaged also in the production of aniline and its derivatives for many years, no such neoplasms, allegedly, had been seen. Rehn attributed this discrepancy to a defective study of workers employed in these factories.

In a discussion of this aspect many years ago Oppenheimer complained that German factories had a tendency to have their workers treated by factory physicians and in their own hospitals. He added that the statements of the workers, among whom such tumors had occurred, differed, according to his experience, widely from those made by the factory physicians. While the information obtained from the workers without any doubt is unreliable as far as the actual figures are concerned, it cannot be entirely disregarded, since it is supported to a certain extent by the observations of Nassauer. This author found 28 cases of tumor of the bladder among 105 workers with a yearly transient index of 15 per cent during the years 1892 to 1904. His statements received confirmation from the report of Leuenberger, who noted that such tumors were 33 times as frequent among dye workers as in the male population of Basel. Similar data were published recently by Mueller (1933) from Basel.

The frequency of aniline tumors (morbidity statistics) in the working population of different factories evidently varies to a certain extent, depending on the types of chemicals used and produced and, especially, on manufacturing processes employed and precautionary measures taken. In addition to these factors which influence the incidence of bladder tumors in different plants, countries and periods, the methods by which statistical data on this subject are obtained are of outstanding importance.

Curschmann in 1920 pointed out that the percentage of aniline tumors among German chemical workers was very low. He found only 177 cases among an estimated 80,000 to 100,000 chemical workers. Scheele, in 1926, attempted to discredit any occupational significance on the causation of bladder tumors in aniline workers by referring to the percentages of such tumors in the surgical patient population of the university clinics of Rostock (1.24), Frankfurt (1.81), Vienna (3.59) and Basel (1.66). He pointed out that these figures did not show any relation to the industrial chemical activities in these cities. He argued, therefore, that in Frankfurt bladder tumors were attributed incorrectly to occupational chemical hazards simply because an appreciable part of the city population was employed in the chemical industry. In support of this contention he quoted the marked variations existing between the proportions of the different occupational groups contributing to the total number of cases of bladder tumor in the various localities (Fuchs, 25 per cent in intellectual workers; Stenius, 38 per cent among agricultural laborers).

The fallacy in this statistical argument is readily evident. It is unessential how high the percentages of the various occupational groups are in regard to the total number of diseased persons in a certain occupational group. Rehn in 1904 estimated that bladder tumors had been observed in between 0.2 and 0.4 per cent of the workers employed at different factories where these conditions occurred. Gehrmann stated that in 532 cystoscopically examined dye workers, engaged in more or less hazardous operations, 25 cases of aniline tumor were detected or 4.5 per cent. Di Maio (1936), on the other hand, found 11 cases among 54 workers (20.3 per cent).

Such figures, however, do not give any reliable information as to the incidence of such tumors in that small group of workers who are engaged in operations in which they receive a more or less continuous and relatively massive exposure (Engel, 1937). The frequency of bladder neoplasms among members of these small groups of operators runs higher (from 80 to 90 per cent), especially when technical and sanitary measures are inadequate. As the number of workers in these particular groups, even in large chemical factories is relatively low, the exceptionally high incidence of bladder tumors among them is not reflected in the frequency rate of neoplasms calculated for the general population of a larger territory in which the plants are located (Mueller (1936) for Basel; Scheele for Vienna).

In more recent years figures of incidence lower than those just quoted have

been published for factories which had been conducted, over a longer number of years, with special technical and sanitary precautions (introduction of a closed production system that eliminates contact with vapors, fumes and dust; extensive exhaust ventilation; careful supervision of repair work; good medical care) (Nassauer; Simon, 1930). Simon mentioned in 1932 that in the report of the German Dye Trust only 21 cases of injuries from nitro substances and amino substances were recorded, adding that he had not seen any new cases of aniline tumor in the last four years. Gehrmann noted that, according to information which he had received from a German plant operating on a closed production system, no new cases had been observed there in the last fourteen years among new workers employed in that time, a remarkable result in view of the period of latency of these tumors.

While it is likely that isolated cases will continue to occur even under the best technical conditions, the frequent, even epidemic-like appearance of cases among the workers of some plants during recent years seems to suggest that the methods of production and the precautionary methods practised in these factories have not conformed with the requirements recognized as necessary from the technical, chemical and medical standpoints. There are still 5 to 6 new cases a year in Germany, according to Staemmler, where the control measures, from the information available, are not only the most thorough and extensive so far undertaken anywhere, but have been in operation over a longer period than in any other country.

While the coal tar dye industry provides by far the chief source of occupational bladder cancers through the contact with dye intermediates (aromatic amino-, and nitro-compounds) and to a lesser degree, with the finished products (dyes) (Maisin), there exists clinical as well as statistical evidence suggesting also that workers of various other trades exposed to pitch, tar, soot, and crude paraffin may be affected by this industrial neoplasm. Analyzing the death certificates of England and Wales for 1921 to 1928, Henry, Kennaway and Kennaway found records of 5621 cancers and 974 papillomas of the bladder in males and 1411 cancers and papillomas of the bladder in females. When the incidence of death from bladder cancer in the general population was taken as 100, there were 15 out of 46 occupations listed which had a score above 150. In five and possibly eight of these fifteen occupations, there was an exposure to coal gas, tar or pitch, in one to lubricating oil and in two to tobacco. The scores in these groups were as follows: patent-fuel workers, 400; gas works engineers, 400; tar distillery workers, 333; cellarmen, 231; lithographic engravers, 231; tobacco manufacturers, 222; gas works managers, 222; gas fitters, 205; brick kiln and oven men, 200; cotton spinners, 198; dyers, 154. Among 65 cases of chimney sweeps' cancer, there was one of the kidney and one of the bladder (Kennaway). Commenting on these studies Burrows, Hieger and Kennaway remarked that the liability to cancer of the bladder in man in certain occupations, in which the incidence of skin

cancer is high, suggested that the same compound might produce both cancer of the skin and of the bladder.

The apparent correctness of this assumption is supported by the observation of bladder cancer in two patent-fuel workers, following the primary development of carcinomas of the skin. Two similar cases were reported by Posner, who saw the combination of scrotal carcinoma and bladder carcinoma in tar workers. A third and fourth case of this type was placed on record by Young and Russell, and O'Donovan, respectively. Bladder cancer in briquette workers was noted also by Sladden. Roesch cited Goldschmidt as having observed a carcinoma of the bladder in a paraffin worker, who had simultaneously a carcinoma of the skin of the upper arm, and a third primary carcinoma of the stomach. The occurrence of bladder cancer in paraffin workers apparently is not extraordinary, as Müller contended that in all cases of this type reported the paraffin workers had been employed previously in aniline factories. The observation of two cases of bladder cancer in tar workers by Sieben is of special interest, as this author emphasized the fact that the two workers did not show any symptoms of chronic arsenic poisoning. The occurrence of a bladder papilloma associated with an ureter papilloma in a gas-plant worker was recorded recently by Renner. The absence of an excessive incidence of bladder tumors in gas-plant workers was attributed by Simon to the existence of good sanitary conditions.

In view of the fact that many of the substances which were held responsible for the above mentioned occupational type of bladder tumor have been incorporated directly, or in a more or less modified form in many foodstuffs, medicinal and cosmetic preparations, or have been used to color toys, paper, wearing apparel and numerous other articles to an ever increasing degree during the last fifty years, it seems to be justified to speculate upon what role these substances may have played in the apparent increase of bladder cancer observed during the same period (Posner). Gurlt recorded only 66 tumors of the bladder (0.39 per cent) among 16,637 tumors occurring at the hospitals in Vienna during 1858 and 1879. During a similar period Hasenclever saw only 3 primary bladder cancers in 7,000 autopsies. An incidence of 0.76 per cent of bladder tumors among hospital patients with neoplasms was reported by Kuester in 1891. The death rate among the population of Basel rose, according to Müller, from 0.007 per cent during 1871 to 1880, to 0.02 per cent during 1901 to 1910, thus, showing a definite and appreciable increase since the establishment of the dye industry in this region. Bollag reported that the relative as well as the absolute incidence of bladder tumors in Switzerland had increased in recent times during successive decades. The mortality rate from bladder cancer represented 1.3 per cent of the total cancer death rate between 1905 and 1910. Surveying the period 1901-1910, Leuenberger, stated that 2.8 per cent of all tumor cases treated (570) in the hospitals of Basel were neoplasms of the bladder.

It is interesting to note that Pack and LeFèvre reached approximately the same percentage (2.74) as Leuenberger, upon analyzing the incidence of bladder cancers among the tumors treated at the Memorial Hospital in New York (1930). The incidence of bladder tumors in males, however, was 4.37 per cent, giving this organ seventh place in the relative incidence of cancers of the various organs. A gradual increase in the number of bladder tumors during the period surveyed was noted also by Henry, Kennaway and Kennaway: In 1921, one hundred and fifty bladder cancers were reported as compared to eight hundred and twelve in 1928; in 1921, eighty-six papillomas of the bladder were listed against one hundred and fifty in 1928.

In an analysis of mortality experience among industrial policyholders of the Metropolitan Life Insurance Company for 1917 to 1935, made by Dublin and Lotka, cancer of the urinary bladder displayed a significant trend of increase among white males and females. The rise of the death rate was more pronounced among men than among women. This observation must be considered as of definite importance, as it was made during a period when the introduction of the cystoscope had made cancer of the bladder accessible to direct observation. There seem to exist, on the other hand, wide geographical variations in this respect. Gaeta found that only 0.6 per cent of all neoplasms observed at the pathologic institute in Milan, Italy, were bladder tumors, while Wilinski reported from Leningrad that 1.76 per cent of all cancers in males and 0.9 per cent of all cancers in females were bladder neoplasms. In a recent report on the cancer mortality in the United States, Hoffman stated that 3.2 per cent of all cancer deaths were caused by bladder carcinoma. A similar ratio was recorded by Young and Russell (3.09 per cent of all cancers).

A reliable interpretation of these figures, at present, is difficult, as numerous factors enter which cannot be gaged properly. It must be conceded that the diagnosis of bladder tumors, that is of neoplasms, which were almost inaccessible to the clinician before the introduction of the cystoscope, was often missed before the turn of the century. The statistical data of that period are therefore less trustworthy than data of more recent date. The important factors of age and sex are rarely considered in the data available. The latter factor appears to be of special importance as bladder cancers are much more frequent in men than women (Pack and LeFévre: 77.8 per cent in males; Joseph: 76 per cent; Matthews: 80 per cent), a discrepancy which may be attributed to anatomical and endocrine sex differences as well as to the fact that men are exposed more often to extrinsic carcinogenic agents of occupational or general environmental character. In spite of the uncertainties stated, evidence supports the belief that the incidence of bladder tumors has increased during the last four decades. This apparent or actual increase coincides with the increasingly extended use of synthetic chemical products containing components of aromatic organic nature, with which large portions of

the general population have come in more constant and increasingly close contact. Future investigations will show whether this relationship is purely coincidental or contains also causal factors.

II. CHEMICAL AND TECHNOLOGICAL ASPECTS

Aromatic amines are compounds consisting of a cyclic hydrocarbon radical (phenyl-, diphenyl-, naphthyl-, tolyl-, xylil-, etc., groups) which replaces one or several hydrogen atoms in an ammonia molecule. They are also called aromatic bases, due to their basic reaction. Aromatic amines may, on the other hand, be considered as uni- or polycyclic hydrocarbons with substitutions of one or several hydrogen atoms attached directly to a ring carbon atom by amino-groups ($—NH_2$). The position of the substitution is designated by the terms ortho-, para-, or meta-. The simplest representatives of this group of aromatic compounds are aniline ($C_6H_5NH_2$) (aminobenzol or phenylamine), and its homologues, toluidine and xylidine. Derivatives of aniline are dimethyl-aniline, paranitro-aniline, diphenylamine, diamino-phenyl (benzidine), etc.

A second type of aromatic amines are compounds with a $—NH_2$ substitution of the kind described above in a complex of two condensed benzol rings (naphthyl-compounds). They are not regarded, however, as amino-derivatives of the benzol series (Engel). Amino-derivatives of benzol and its homologues, as well as of naphthalene, are not those aromatic compounds which have the nitrogen contained in an azo- ($—N=N—$) group, diazo ($=N\equiv NH$) group, and hydrazin ($—(NH—NH_2)$) group. Only a few of the synthetic dyes are aminobenzol derivatives, such as oxidation black, phenylene diamine (ursol), aurantia (hexanitro-diphenylamin), among the simple substances of this type, and the various di- and triphenylmethane dyes and azo-dyes with phenyl-groups possessing free, that is, not diazotized, alkylized or arylized amino-groups.

Aniline and its homologues are manufactured by the reduction of nitrobenzol or of the corresponding nitro-compound, respectively, by the action of hydrochloric acid and iron shavings or by the contact process.

While pure aniline is a colorless oily liquid with aromatic odor, crude aniline has a yellowish to brownish color. An increasingly deep brownish color also develops in pure aniline through a slow oxidation process active when in contact with air. The molecular weight of aniline is 93.07; specific gravity 1.0254 at 15°C; boiling point 189°C; and the melting point 5.96°C. A saturated aqueous solution contains at 16°C 3.2 per cent aniline (or 34.8 parts aniline per volume in 1000 parts of water), conversely 1000 parts of aniline will take up 52.22 parts of water (approximately 5 per cent). Aniline is easily soluble in all proportions in ether, acetone, benzol, fats, oils, carbon disulfide, etc. An aqueous solution of aniline is weakly alkaline. Aniline denatures protein, but its salts do not exhibit this property. The salts of aniline

are, on the other hand, readily soluble in water and usually give an acid reaction. Aniline and its derivatives are extensively used in the production of various dyes (tri-phenyl-methane dyes and azo-dyes and especially artificial indigo), of medicinal preparations (antifebrin, phenacetin, pyrazolon-derivatives, etc.), in the rubber industry as an accelerator of vulcanization, and for aniline black dyeing (Ullmann, F.).

Benzidine ($C_{12}H_{10}(NH_2)_2$) (diamino-phenyl), an aniline derivative, is the second compound of major importance in regard to the chemical etiology of bladder tumors. It is a white, solid substance having a slightly alkaline reaction. This compound is soluble in water in the ratio of 1 part of benzidine in 244 parts of water at 17°C. One part of benzidine is soluble in 45 parts of ether and is readily soluble in alcohol. It can be easily oxidized. Nitric acid transforms benzidine into a diazo-compound. The sulphate salt is almost insoluble in water. Benzidine is produced from nitrobenzol by an intermediary step over hydrazo-benzol. Nitrobenzol first is reduced by zinc and sodium hydroxide to hydrazo-benzol ($C_6H_5NH—NHC_6H_5$). When this compound is treated with mineral acids, it undergoes an intramolecular rearrangement, forming thereby benzidine. During the course of this process, aniline is formed as an impurity. Benzidine is used for the manufacture of different dyes, such as congo red, diamine blue, diamine red, diamine black, benzopurpurin, or dianisidine blue.

The third group of aromatic compounds, possessing considerable etiological carcinogenic significance, are the naphthylamines, of which two types exist, the alpha-naphthylamine and the beta-naphthylamine ($C_{10}H_9NH_2$). They are produced by the reduction of the corresponding nitro-naphthalenes. The beta-naphthylamine is usually prepared by the action of ammonia upon beta-naphthol in an autoclave under pressure. Beta-naphthylamine is slightly soluble in water (1.17 per cent in cold water), but very soluble in alcohol, ether and oils. Its melting point is 112°C and thus is a solid at ordinary temperature. The white substance is almost odorless, giving off a faint sweet aromatic odor. Upon exposure to air, it slowly oxidizes, first becoming pinkish and, later, orange brown in color. The alpha-naphthylamine is insoluble in water and soluble in alcohol, ether and oils, and sublimates. Its melting point is 40.3°C (Ullmann, F.). The white, solid matter has a fecal odor and turns red upon contact with air.

Both naphthylamines are not appreciably volatile in air or steam, but are more volatile in superheated steam, and very volatile in overheated steam in vacuum.

They are mainly used in the production of dyes. Small amounts of alpha- and beta-naphthylamine are employed as accelerators in the vulcanization of rubber, and together with xylidines and toluidines for the flotation of ores. Formyl- and glycin-derivatives of beta-naphthylamine as well as formaldehyde and acetaldehyde condensation products are used as preservatives of rubber and as adjuvants in the tanning industry.

Dublin listed the workers of the following occupations among whom bladder tumors of industrial origin may occur: aniline workers, artificial leather makers, calico-printers, coal-tar workers, compositors, compounders (rubber); dye makers, explosive workers, feather workers, lithographers, millinery workers, mixers (rubber), painters, paint makers, pencil (colored) makers, photographic workers, pressroom workers (rubber), printers, reclaimers (rubber), rubber workers, tannery workers, vulcanizers. Thus aniline, benzidine and naphthylamines are industrially important chemicals.

III. ETIOLOGICAL AGENTS

The question concerning the chemical character of the carcinogenic agents causing these vesical neoplasms is still controversial in spite of the fact that tumors of this type have been known for more than forty years. While Rehn attributed the development of such tumors only to fuchsin, which is made by melting aniline, toluidine, nitrobenzene and iron chloride, subsequent investigators have added a large number of substances to the list of suspected carcinogenic agents. The great difficulties which confront the investigator in this respect were pointed out by Hamilton: 1) Workmen handle usually more than one compound and are often shifted from one department to another. 2) Different degrees of danger exist with the same compound when different processes are used. 3) Certain impurities or by-products which occur in traces and are often unsuspected may be more harmful than the parent substance. 4) The nature of the dyes and the methods of producing them vary in different factories.

It was soon recognized, however, that the appearance of bladder tumors was often associated with prolonged occupational contact with the following aromatic bases: phenylamine (aniline), its isomers and homologues (toluidine and xylidine) and other amino derivatives; diphenylamine (benzidine), its isomers and derivatives (e.g., tolidine or dianisidine); naphthylamines and related compounds (e.g., naphthylene diamines). The contention of Nassauer, that aniline alone was the carcinogenic agent since it was presumptively contained as an impurity in all other substances incriminated, has no basis in fact.

In addition to these basic substances, various and numerous intermediary products (secondary and tertiary arylated and alkylated aromatic amines, such as dimethylaniline), formed during the production of dyestuffs, have been claimed repeatedly to be carcinogenic (Engel, 1937). In this connection attention may be called to the many impurities occurring in the commercial aromatic amines, such as beta-beta-dinaphthylamine, alpha-beta-naphthazine, 1,5- hydroxynaphthalene and various other related substances (benzcarbazoles) (Hueper, Briggs and Wolfe; Boyland and Brues; Cook and associates).

The various possibilities as to the formation of such impurities during the production of aromatic amines were investigated by Boyland and Brues. They

found that during the process of alpha-naphthylamine formation, by the reduction of alpha-naphthol through the action of iron and small amounts of hydrochloric acid, conditions exist which permit the development of small amounts of hydrazonaphthalene. This compound in turn may undergo in the presence of acid a benzidine change, resulting in the formation of two substances, one of which may condense into 1.2.7.8-dibenzcarbazole. If the alpha-nitro-naphthalene contained any meta-nitro-naphthalene, this may undergo similar changes to form 3.4.5.6-dibenzcarbazole.

When beta-naphthylamine is manufactured under pressure at a temperature of 150°C, an excess of heat or insufficient stirring may lead to the formation of beta-beta-dinaphthylamine, representing a contaminant of the crude beta-naphthylamine. When this is distilled in vacuo for purification, 3.4.5.6-dibenzanthracene may be formed. Carbazoles are also formed in the distillation of diphenylamine. The presence of alpha-naphthol may lead to the formation of alpha-beta-dinaphthylamine and that, in turn, to 1.2.5.6-dibenzcarbazole. A probable contaminant of beta-naphthol is beta-beta'-dihydroxy-alpha-alpha'-dinaphthyl which, when heated with zinc and ammonium chloride, yields 3.4.5.6-dibenzcarbazole. Naphthylamine workers may thus come in contact with dinaphthylamines and dibenzcarbazoles contained as impurities in the basic products. All aromatic amines, with the exception of the sulfonates, aminoanthraquinones and the more complex derivatives, irritate the bladder and therefore are suspected of possessing carcinogenic qualities (Engel).

Not only the basic and intermediate substances used in the production of dyestuffs but also the finished products, the dyes, have been mentioned by several authors as causative factors (Curschmann; Schwerin; Oppenheimer, 1920 and 1927, Schueller, and others) (fuchsin, rubin, palatin black, rhodamin, aminonaphthol red, patent blue, pure yellow, congo red, benzopurpurin, dianisin, safranin, blue rosaniline dyes, eosin, aniline black and various other azo-and diazo-dyes). A definite decision on this matter is not possible at present for all dyes incriminated, as some of the dyes often contain aromatic amines as impurities, especially basic dyes of the azin series (e.g., nigrosine, indulin or safranin), or aromatic amines are used as dye mordants or oxydizers in the dyeing process (e.g., aniline black).

It must be pointed out that there is no record in the literature of extensive, systematic and reliable investigations on the potential carcinogenic properties of synthetic dyes, especially of those which may be decomposed in the body into their aromatic amine constituents (Hueper, 1934; Shear) and thus may produce chronic metatoxic effects. A thorough study of this question appears to be highly desirable, as dyes of this type, such as yellow OB (ortho-toluene-azo-beta-naphthylamine) have been used extensively for some time in the artificial coloring of foodstuffs (Traub, Gordon and Van Dyke; Climenko; Schwartz; Editorial, *J.A.M.A.*), and in view of the fact that dyes chemically closely related (amino-azo-benzol, amino-azo-toluol, light green, o- and

m-dimethyl-azo-benzol) recently have been employed successfully in the production of malignant tumors of the connective tissue, liver, stomach, and bladder (Shear; Schiller; Yoshida; Otsuka and Nagao; Yamazaki and Sato).

Attention may be called to observations made many years ago by Salant and Bengis, who experimented with various related dyes (yellow AB (benzene-azo-beta-naphthylamine), yellow OB (toluene-azo-beta-naphthylamine), sudan III (benzene-azo-benzene-azo-beta-naphthol), sudan I (benzene-azo-beta-naphthol), butter yellow (benzene-azo-dimethylaniline), oil yellow (benzene-azo-phenol), sudan G (benzene-azo-resorcinol) and spirit yellow (amino-azo-benzene)). The introduction of these dyes either orally, subcutaneously, intravenously or intraperitoneally, into rats, rabbits and cats resulted in their retention in the adipose tissue. The dyes remained longer in this tissue than in any organ and the degree of retention, as well as excretion by the urine, ran parallel to the amount of dyes given (ranging from days to weeks).

A satisfactory agreement also does not exist in regard to the carcinogenicity of the three aromatic amines mainly incriminated (aniline, benzidine and naphthylamine). There is a general consensus that beta-naphthylamine, at least in its commercial form, is definitely cancer producing. There is still doubt as to alpha-naphthylamine. While German investigators are doubtful as to this substance and have listed only a few cases in which it was suspected as the activating agent (Engel, 1937), the American authors have attributed, with certain reservations, an appreciable portion (about 25 per cent) of the total number to this substance (Gehrmann; Evans). It is, however, uncertain whether alpha-naphthylamine possesses cancer-producing qualities to any appreciable degree, as the commercial product of German, American and English manufacture contains from 5 to 10 per cent beta-naphthylamine as an impurity (Engel, 1937; Gehrmann). The latter substance may account for the carcinogenic response displayed after contact with commercial alpha-naphthylamine.

The potential carcinogenic role of aniline appears to be equally uncertain if the statements of German and American investigators are compared. While the German sources are definite as to the carcinogenic qualities of this compound (Engel, 1937) and list 78 cases as caused by it and its homologues, the American authors (Gehrmann; Evans) are equally emphatic that, according to their observations, the American product does not produce tumors. Evans stated that there was not a single case of tumor of the bladder in a group of 65 men who had been engaged for as long as twenty years in the production of aniline exclusively. The average time of employment of these men was twelve years. They suffered, moreover, frequent attacks of acute aniline poisoning (Wolfe).

It is also doubtful, whether pure benzidine base is carcinogenic. According to German sources, none of the workers of a plant in which men came in

intimate cutaneous contact with great quantities of powdered benzidine base for many years showed bladder tumors. On the other hand, it is well established that workers engaged in the production of this compound frequently contract vesical neoplasms. Engel (1937) listed 25 cases in a series of 190 as of benzidine origin and Evans listed 13 cases of a total of 83 as of this origin.

The carcinogenicity of aromatic nitro-compounds has been disputed by Engel, who contends that their mistaken incrimination is attributable to the fact that they are used for the production of the corresponding amino-compounds. A reinvestigation of this question appears to be indicated in view of the recent report of Schwartz, who noted the occurrence of bladder tumors among workers of an American chemical plant in which dinitrophenol was handled. Barkmeyer mentioned also an aniline tumor in a worker exposed to nitrobenzol. Naphthols appear to be harmless (Oppenheimer), as only a single case of bladder tumor has been observed so far in a worker of a naphthol factory (Posner).

A quite different explanation regarding the causation of bladder tumors was proposed by Bayet and Slosse, and Hamilton. They claimed that bladder tumors in dye workers were the result of a chronic arsenic poisoning. It may be either caused by the inhalation of hydrogen arsenide generated during the manufacture of aromatic amines, or introduced into the body by skin contact, or in the form of dust into the lung during the handling of these substances, or of the finished products containing arsenic as an impurity. The contention was based on the demonstration of arsenic in the urine of the dye workers and upon the known carcinogenic properties of arsenic.

The following description of the premonitory symptoms of chronic aniline poisoning in connection with bladder tumors is given by Bayet. The earliest, most characteristic symptom is profuse sweating of the hands, with swelling of the back of the hands. This is followed by an eczema with occasional loss of the deeper tissue. These lesions of pea-size are sharply outlined and are similar to those that occur on the arms of paraffin workers. In instances, this is followed by more acute cutaneous affections, such as general edema of the hand, face, ears and, especially, of the penis and scrotum. In some workers handling aniline, hyperkeratoses, which had the appearance of papillomas, were noticed. Because of this similarity of the cutaneous manifestations of chronic aniline poisoning with those seen in arsenic dermatitis, Bayet concluded that both conditions had the same etiology, namely, arsenic. This substance also was claimed to be responsible for the tumor formation caused by tar and related substances. Hamilton supported this contention and pointed out that the absence of bladder tumors among chemical workers in the United States was attributable to the fact that in the American dye factories the production of benzidine did not involve any risk of arsenic poisoning because manufacturing methods differed from methods in Germany and England. It is correct that arsenious acid was used formerly as an oxidative

agent for the oxidation of aniline in the fuchsin operation. As the complete removal of the arsenic from the finished product was complicated and expensive, this was often omitted for economical and competitive reasons. A small amount of arsenic remained in the dye and later became attached to the fiber of the fabric or material dyed (wool, silk, cotton, leather, feathers, paper, liquor, wines, ink, or pencils) and was the source of many arsenic poisonings. In more recent years arsenic has been replaced in this process by nitrobenzol dissolved in sulfuric acid. While nitrobenzol is also poisonous, it can be removed easily from the finished product by evaporation. Arsenic poisoning therefore can not be the cause of those bladder tumors occurring in later years.

The contention of Bayet and Slosse, as well as of Hamilton has been attacked on clinical and statistical grounds by various authors (Berenblum; Posner; Henry, Kennaway and Kennaway; Ullmann; and others). It is known that arsenic may cause skin cancer but not, as a rule, bladder cancer. The only possible exceptions presumably were observed by Janssen; and Goeckermann and Wilhelm. Janssen recorded the occurrence of bladder tumors in individuals treated with arsenic and tar for psoriasis. Even here it appears more probable that the tar has played the major role in eliciting the neoplastic response in the bladder. Goeckermann and Wilhelm reported a case in which the common hyperkeratotic cutaneous lesions of the palms, soles and trunk, suggesting in part Bowen's disease, were present in association with papillomas and carcinoma of the ureter and the bladder. Arsenic was demonstrated by microchemical and histochemical methods in the hyperplastic and neoplastic manifestations. The authors suggested that the vesical lesions were caused by the action of a hematogenously distributed arsenic. Kennaway has pointed out, however, that it is not clear why arsenic should produce *cancer of the skin in a pitch worker*, but *cancer of the bladder in an aniline worker*. In view of the fact that Bayet himself later abandoned his theory of the arsenic nature of tar cancer, there does not remain a valid reason for considering in the future arsenic poisoning as a potential and common cause of aniline tumors.

There remain two more theories to be mentioned, chiefly for completeness of this account, as they do not possess scientific or practical value. The presence of an excessive amount of oxalic acid in the urine of dye workers and animals exposed to aromatic amines led Huldschiner to assume that the bladder tumors of dye workers were the result of a continuous mechanical irritation of the bladder mucosa by the sharp edged oxalic acid crystals. A theory, similarly unusual, was proposed by Green who contended that among other occupational cancers, aniline tumors of the bladder were caused by the chronic inhalation of sulfur dioxide generated in the plants during the production of dyes.

IV. EXPERIMENTAL ANILINE TUMORS

Numerous unsuccessful attempts have been made to reproduce these aniline tumors in animals by exposing the latter over prolonged periods and through

different routes to the various aromatic amines (Grandhomme; Jaffé; Schwerin; Posner and Huldschiner; Fischer; Askanazy; Oppenheimer, 1926-1927; Adler; Henkel and others). In these experiments various animals were used (mice, rats, rabbits). The mortality among the animals was high. Postmortem examinations showed inflammatory conditions in the lungs and fatty degeneration of the liver and kidneys. With the exception of the temporary acute and the chronic inflammatory and hyperemic conditions in the mucosa of the bladder, nothing was seen indicating a neoplastic response to the substances used. Burrows, Hieger and Kennaway were unsuccessful in their attempt to produce bladder tumors in mice subcutaneously injected with 1.2.5.6-dibenzanthracene.

The more recent attempts of Leitch, Kennaway and Fry to produce bladder tumors in mice and guinea pigs by the treatment with aniline, benzidine, fuchsin, scarlet red, alpha- and beta-naphthylamine were negative. Repeated applications of 1.2-hydronaphthoquinone to the skin of mice similarly were without neoplastic response. Berenblum and Bonser also failed to produce bladder tumors in rats maintained on a diet containing 85 per cent marmite, 5 per cent beta-naphthylamine, 5 per cent alpha-naphthylamine and 5 per cent aniline (spread on bread for one series and on meat for a second series). This management was continued in the first series for an average of 28 weeks (4 to 76 weeks), and in the second series for an average of 46 weeks (25 to 57 weeks). A third group of rats inhaled vapors of 5-chloro-o-toluidine for two hours daily, showing an average survival period of 25 weeks (3 to 45 weeks). Except for some congestion of the blood vessels, occasional ulcerations of the mucosa, leucocytic infiltrations, and hemorrhages in the submucosa, the bladders of these rats were normal.

Brief mention may be made of the experiments of Climenko on rabbits and dogs fed with o-toluene-azo-beta-naphthol and toluene-azo-beta-naphthylamine for periods up to three months. There were no pathological changes of any kind in the urogenous organs of these animals. In view of the insufficient time of exposure, a negative outcome could be anticipated.

More recent experiments of Schär (1930), and of Perlmann and Staehler (1932 and 1933), were somewhat more promising, but the results could not be confirmed by Berenblum and Bonser, or by Hueper, Briggs and Wolfe. In Schär's experiments, 16 young rabbits inhaled ethyl-beta-naphthylamine hydrochloride, phenyl-alpha-naphthylamine hydrochloride, alpha-naphthylamine and beta-naphthylamine, respectively, for periods of between six and twenty months. The concentration of the dust was low, so as to imitate plant conditions. At the end of the experimental period, one animal, which had been exposed to alpha-naphthylamine, showed a lesion in the bladder which was interpreted as a fibrous polyp; and a second rabbit revealed epithelial changes in the vesical mucosa which were considered as carcinomatous.

These diagnoses, however, have been doubted seriously on various grounds

by several authors (Stewart; Berenblum). Perlmann and Staehler, who also employed rabbits but administered beta-naphthylamine and aniline, respectively, by daily subcutaneous injections, obtained, after several months (from six to thirty-four weeks) of treatment, fibro-epithelial papillary formations in 7 of the 70 rabbits used. Four of the papillomas were present in a series of 40 rabbits treated with beta-naphthylamine, while another was found among 30 animals exposed to aniline. This experiment has been repeated recently by Berenblum and Bonser, as well as by Hueper, Briggs and Wolfe, without positive results. The period of exposure and the dose employed in these duplications were even larger than those in the original experiments of Perlmann and Staehler.

Berenblum used 98 rabbits which were injected once a week intraperitoneally with watery suspensions of 1 per cent benzidine (15 cc.), 1 per cent alpha-naphthylamine (15 cc.), 1 per cent beta-naphthylamine (15 cc.), 26 per cent solution of aniline (15 cc.) and 1 per cent solution of 5-chloro-o-toluidine (20 cc.), respectively. The number of injections varied in the individual animals ranging from 52 to 76. Fifty-three rabbits survived more than 6 months and some as long as four years. Hueper, Briggs and Wolfe employed fifteen rabbits which received daily intraperitoneal injections of 3 mgm. beta-naphthylamine for a period of nine months. Berenblum attributed the failure to produce bladder tumors in rabbits to the following two possible factors: The particular species may be unable to synthesize the carcinogenic compounds or it shows lack of response on the part of the bladder to the compound formed. While such considerations may be correct, definite proof is lacking that rabbits are refractory to bladder tumor formation in response to aromatic amines. Attempts should be made to produce these neoplasms by feeding large amounts of aromatic amines.

In the experience of the author the average rabbit tolerates well large doses of beta-naphthylamine given orally over a period of several months (125 mgm. daily). There may exist, however, fundamental differences in the reactivity to or metabolic degradation or detoxication of these substances between rabbits, dogs and man. Berenblum noted that rabbits react upon the introduction of benzidine with hematuria, while dogs develop glycosuria (?) (glucuronic acid reduction? (hepatic injury?)). In the urine of both animals there is an iron containing pigment giving to the urine a dark color (Adler). Experiments demonstrated that the methods through which 2-amino-1-naphthol ethereal sulfate could be extracted successfully from the urine of dogs fed with beta-naphthylamine were of no avail in this respect as to the urine of rabbits. Such discrepancies, apparently, depend upon differences in the metabolic degradation of aromatic compounds in herbivorous and carnivorous animals, respectively. It has been observed, for instance, that herbivores (rabbits) oxidize acetanilid ($C_6H_5NHC_2H_3O$) in the para-position forming 1-aminophenol conjugated with sulfuric acid and glucuronic acid, splitting

off the acetyl group. This urinary metabolite is obtained entirely in the alkaline fraction during extraction of the urine, while the acid fraction does not contain any part of it. On the other hand, when acetanilid is introduced into carnivores, only traces of p-aminophenol are isolated from the basic extract. The main part of the metabolized chemical appears in the acid fraction as o-oxycarbanil paired with the two acids above mentioned. The oxidation in this case takes place in the ortho-position without elimination of the acetyl group forming first the unstable o-oxyphenylcarbaminic acid, which spontaneously changes into o-oxycarbanil. It appears not unlikely that differences of this kind may determine variations in the susceptibility of different animals to the same carcinogenic chemical.

Hueper, Wiley and Wolfe produced papillomatosis and carcinomatosis of the bladder in female dogs by daily subcutaneous and oral administration of beta-naphthylamine (from 300 to 450 mg. daily in capsules) for from twenty to thirty-two months. The lesions observed in cystoscopic and histologic examinations of the bladders of 12 of the 16 dogs thus treated were identical with those seen by these authors in cystoscopic and histologic examinations of dye workers. The tumors continued to grow and become more numerous in some of the dogs after discontinuation of the treatment during the last six months of observation, while in one dog the first neoplasms in the bladder were noted several months after cessation of exposure. The termination of contact with the carcinogenic agents thus was followed by progression in the appearance and development of the neoplastic manifestations. While none of the 5 dogs which have been killed so far has shown any metastatic deposits at autopsy, one dog presented, on histologic examination, neoplastic penetration into the subserosa of the vesical wall. The recent statement of Ferguson in regard to previous experimental production of bladder tumors in dogs is incorrect and apparently based on faulty translation and interpretation of cystoscopic observations made by Engel (1924) during acute experiments with naphthylamine poisoning.

Berenblum and Bonser, as well as Hueper, did not succeed in producing skin tumors in white mice painted for nine months with an ether extract of urine obtained from dye workers with bladder tumors and from dogs treated with beta-naphthylamine. This failure may be ascribed to several possibilities. The amounts of carcinogenic substances in the urine might have been too small to be effective even after concentration. The chemical manipulation of the urine necessary for extraction might have produced a fundamental change in the chemical and biologic properties of these metabolites. The skin of the mouse might possibly be a less sensitive tissue than the mucosa of the bladder of man or of the dog.

Boyland and Brues tested the following substances which they suspected as normal impurities in the various carcinogenic aromatic amines: alpha-alpha-dinaphthylamine, beta-beta-dinaphthylamine, 1.2.5.6-dibenzcarbazole, 1.2.7.8.-

dibenzcarbazole, 3.4.5.6-dibenzcarbazole. These compounds were dissolved in benzene and applied to the skin of mice. Carcinogenic responses were obtained with 1.2.5.6-dibenzcarbazole and also, to a lesser degree, with 1.2.7.8-dibenzcarbazole. In addition to the skin tumors, there were present also hepatomas (cholangiomas). Colloidal suspensions of 3.4.5.6-dibenzcarbazole injected subcutaneously into rats resulted in the formation of sarcomas. Bladder tumors were absent in both mice and rats.

Recent experiments of Japanese investigators have demonstrated that not only dye intermediates, but also the finished products may produce bladder tumors in animals when given orally. When rats were fed with a diet of unpolished rice to which 2-amino-5-azotoluene had been added, they developed not only hepatomas and cholangiomas, but some of them exhibited also papillomas of the bladder (Sasaki and Yoshida; Yoshida). Similar results were obtained with rats kept on an unpolished rice diet with the addition of 0.2 per cent ortho-meta-dimethyl-azo-benzol (Otsuka and Nagao). There was a papillomatosis of the bladder in 13 animals surviving the treatment for more than 122 days. In seven of these rats, the papillomatosis was complicated by infiltratively growing, non-papillomatous tumors of spindle cellular structure. The blastogenic effect of the diet upon the bladder was less pronounced when ortho-meta-dimethyl-azo-benzol was replaced by 4′ oxy-3.3′-dimethyl-azo-benzol. The two last mentioned chemicals did not exhibit any special affinity to the liver, such as observed in the case of 2-amino-5-azo-toluene, which is responsible also for the production of papillomas in the forestomach of the rat. More recent investigations reported by Kinosita dealing with the oral and subcutaneous administration of various aromatic amines and azo-dyes to rats and guinea pigs enlarged the number of substances exerting a proliferative response upon the urogenous epithelium. Alpha-naphthylamine given by mouth caused in guinea pigs epithelial proliferation and keratinization of the renal pelvis and, when injected subcutaneously, papillomas of the bladder. Otsuka and Nagao obtained bladder papillomas in rats after the oral feeding of 4′-acetoxy-2.3′-dimethyl-azo-benzene and of 4′-carbo-methyoxy-2:3′-dimethyl-azo-benzene. Kinosita stated that many tolueno-compounds are apt to cause bladder papillomas. Nagayo and Kinosita observed the development of bladder papillomas in rabbits, guinea pigs and rats after the subcutaneous injection of alpha-naphthylamine and following the oral administration of some azo-compounds. Morigami and Nisimura reported recently that o-toluidine in oil injected subcutaneously into rabbits caused the development of bladder papillomas, while a similar administration of benzidine produced atypical epithelial proliferations in the vesical mucosa.

In general rats are not suitable for the study of experimental tumors of the bladder, as they suffer frequently from spontaneous and sometimes very extensive papillomatosis of the bladder caused by infestation with worms (Trichosomoides crassicauda) which lodge in the epithelial lining and elicit

solid epithelial papillary formations without any participation by, or simultaneous changes in, the submucosal connective tissue during the early stages (Watanabe, 1934; Löwenstein, 1910 and 1911; Hueckel). These papillary changes remain benign. It would be, however, of interest to know whether they may be transformed into malignant ones on coming in contact with the urinary metabolites of the compounds used by the Japanese workers, in analogy with the malignant changes produced by Rous in the Shope rabbit papilloma after local treatment with scarlet red. These considerations also must be applied to the report of Brancati, who found a broad-based papilloma at the posterior vault of the bladder in a rat fed for one year with aniline blue (arylrosaniline dye).

Attempts to produce such a transformation in the bladder of rats, infected with Trichosomoides crassicauda and showing a vesical papillomatous hyperplasia, by the administration of oestron given over a period of 47 to 465 days (total amounts ranged from 2,085 gamma to 25,920 gamma) were unsuccessful.

It may finally be mentioned, that Beck reported the production of a marked papillomatosis of the urinary bladder of rabbits which had been treated for a period of 10.5 months by repeated intravenous injections of an emulsion of a detoxicated tar. Beck attributed these lesions to the presence of tar excreted in the urine. This observation is of a certain significance, as claims have been advanced concerning the occupational genesis of bladder cancer in tar workers.

In addition to these attempts to produce bladder neoplasms by systemic exposure of animals to aromatic chemicals, numerous experiments have been made to elicit tumorous responses by placing foreign bodies of widely differing chemical composition directly into the bladders of animals. T. Bauer, making a separate pouch in the bladder of the rabbit and painting the mucosa of the pouch for several months with a mixture of tar, scarlet red, aniline and soot, observed the development of papillomas with epithelial metaplasia but without malignant changes. Maisin and Picard introduced into the bladders of rats by cystostomy small plugs consisting of equal parts of tar, paraffin and scarlet red. In 66 per cent of these animals, diffuse papillomatosis was seen after the lapse of one month and a half. The tumors were considered, in part, "histologically malignant", as they showed infiltrative growth. Similarly, the introduction of pellets, consisting of tricresol and aniline oil, into the bladder of rabbits by Roffo resulted in the development of a vesical papillomatosis. Leone placed in the bladders of guinea pigs and mice pellets of tar, cement, asphalt and licorice. These implantations were followed by metaplastic and keratinizing epithelial changes, with development of papillary processes and infiltrative epithelial growth into the muscular layer under a formation of epithelial cysts. The processes were interpreted as precancerous. By laparotomy, Watanabe (1934) inserted into the bladders of white rats pellets composed of a mixture of tar, scarlet red and paraffin. In 9 of 55 rats thus treated

and surviving, he found marked proliferation of the vesical mucosa, which he considered as probably malignant, since alveolar epithelial nests were seen within the muscularis.

A critical analysis of the experimental conditions observed in these investigations throws some serious doubt on the value of the results as contributions to the knowledge of the causative mechanism of bladder tumors. The use of a mixture of substances of undetermined chemical and physical character, the presence of surgical trauma of the bladder and the possibility, if not even the probability, of the pre-existence of parasitic papillomatosis of the bladder are complicating factors which interfere greatly with a reliable interpretation of the results reported.

On the other hand, the recent experimental studies of Yamazaki and Sato, who made daily injections of watery solutions of aniline (1 per cent) and of olive oil solutions of ortho-amino-azo-toluene (1 per cent) into the bladder of male rabbits over an extended period, are of much greater value and significance. Twelve out of thirty male rabbits receiving aniline water instillations showed papillomatous tumors in the bladder after 13 to 362 days of treatment. The papillomatous tumors were located in the apex of the bladder and represented gyriform, warty elevations. The stalks were very vascular, fibrous and lined by a stratified, large, polygonal epithelium. In the majority of cases inflammatory reactions were absent. The papillomas in the two rabbits receiving intravesical injections of the ortho-amino-azo-toluene in olive oil appeared after 119 and 208 days, respectively, of treatment. Seven additional rabbits belonging to this series remained normal. Three out of six rabbits which were treated with intravesical instillations of a saturated watery solution of ortho-amino-azo-toluene developed bladder papillomas after 48, 198 and 248 days, respectively, of treatment. While the subcutaneous injection of watery solutions of aniline and ortho-amino-azo-toluene, respectively, into rabbits did not result in the production of neoplasms in the bladder, tumors in this organ were observed in three rabbits which received daily subcutaneous injections of a 1 per cent solution of ortho-amino-azo-toluene in olive oil. The results reported are remarkable in view of the extremely short period which apparently was needed to elicit the neoplastic response in the bladder in several animals (13 days!).

It may be mentioned that the gross appearance, as well as the histological structure of the tumors described, seemed to resemble closely the hyperplastic villous areas located also at the apex of the bladder, reported by Hueper, Briggs and Wolfe, following the subcutaneous administration of solutions of beta-naphthylamine. These authors suggested that the apical vesical lesions might represent estrogenic responses, as they were observed repeatedly in female rabbits which had developed a pseudo-pregnancy reaction with lactating hyperplastic mammary glands following periodic vaginal manipulations when cystoscopically examined. The occurrence of bladder

tumors in mice painted with 1.2.5.6-dibenzanthracene plus theelin, by Perry and Ginzton, furnishes an additional suggestion concerning a possible relationship between the action of female sex hormone and hyperplastic and neoplastic processes of the bladder mucosa. Lacassagne also reported the appearance of verrucous hyperplasias at the apex of the bladder of mice treated with estrone.

Recent investigations have shown also that tumors of the kidney and renal pelvis can be produced experimentally by the introduction of the chemical agents above mentioned into this organ. The deposition of pellets of tar and concrete into the renal pelvis of guinea pigs and rabbits (Latteri) was followed by the development of papillomatous vegetations, leukoplakia and adenocarcinoma of this organ. When pellets of cholesterol containing 1.2.5.6-dibenzanthracene were placed into the kidneys of mice, renal carcinomas of the epidermoid type developed in 12 animals (Ilfeld). These neoplasms seemed to originate from the renal pelvis and had an incubation period of nine months. Fourteen additional mice treated identically showed only inflammatory lesions. The animals which had received the largest doses of dibenzanthracene developed the earliest tumors.

V. CAUSATIVE MECHANISM

The carcinogenic aromatic amines mentioned may enter the organism through three systems: the respiratory, the alimentary and the cutaneous. The majority of investigators agree that the main entrance is through the lung, because of the inhalation of these substances in the form of fumes or dust (Rehn, 1906; Oppenheimer, 1920; Nassauer, and others). The gastrointestinal tract usually is discounted as a place of resorption of major significance on account of the general precautionary measures taken by the workers in chemical factories, such as washing the hands before handling food (Leuenberger), and because of the low solubility of these compounds in water, which impairs their resorption through the intestinal mucosa. Gehrmann has pointed out justly that whenever such precautions are not taken, owing to ignorance or negligence, gastrointestinal resorption may add to the amount of these substances entering the body through the lungs and skin. A part of inhaled dust, moreover, is swallowed and thus enters the gastrointestinal tract. It seems also to be doubtful, whether the low solubility of the aromatic amines in water acts as a preventive to resorption in the intestine, as fatty substances are usually present in sufficient amounts to serve as solvents and thereby facilitate penetration into and through the mucosa. It can be shown easily that acute as well as chronic poisoning of animals can be obtained readily with oral feeding of the aromatic amines. The absence of these compounds from the feces excreted is additional proof of their effective resorption.

As all aromatic amines are soluble in lipoids they penetrate the skin rapidly, a fact which is demonstrated satisfactorily by the numerous cases of acute

aniline poisoning observed among workers following cutaneous contact with aniline and by the accidental occurrence of such poisonings on the wearing of shoes dyed with compounds containing aniline. Cutaneous absorption of appreciable amounts of naphthylamine and benzidine is not likely to occur under ordinary occupational conditions as these substances are solids.

In the present state of knowledge no definite decision is possible, as to whether the aromatic amines as such or their organic oxidized conversion products are responsible for the carcinogenic action. Conversion products have been demonstrated in the urine for aniline, dimethyl-aniline, benzidine and both naphthylamines (Engel, 1920, 1924 and 1927). They are partly excreted as aminophenols, partly as aminonaphthols. Klingenberg showed that aniline is hydroxylized in the body and excreted with the urine as para-amino-phenol ether sulfate (Schmiedeberg), a substance considered by Leuenberger as the main carcinogenic agent. Engel (1920 and 1924) pointed out that there are several aromatic bases suspected of carcinogenic qualities which do not undergo this change in the body (e.g., para-toluidine) because the para-group can be hydroxylized only into an amino group when the para position is not occupied by another group (methyl-group in para-toluidine). Adler, however, reported that benzidine and substances with occupied para position when fed to rabbits and dogs undergo hydroxylization. The controversy was settled finally by Weber and Heidepriem, who could show that the results of Adler were due to the use of unsuitable methods of extraction and therefore incorrect. Rambousek, on the other hand, asserted that the aniline derivatives excreted with the urine in partly or completely detoxicated forms are not the dangerous fractions, but that the part which is responsible for the injurious effect is the 1 per cent of the total amount introduced which remains in an unchanged form in the blood, leaving the body with the respiratory air.

Engel (1920 and 1924) concluded from acute experiments, in which he gave dogs large amounts of beta-naphthylamine, that this substance is transformed quantitatively in the body and excreted with the urine as a univalent or bivalent aminonaphthol bound to sulfuric acid or glycuronic acid. This statement, however, is open to doubt, as Engel calculated the amount of aminonaphthol excreted indirectly from the amount of sulfuric and glycuronic acids found in the urine. The procedure must be considered as a rather unreliable one in view of the fact that the introduction of manifestly toxic doses of beta-naphthylamine causes degenerative changes in various organs (liver, kidney, spleen, lymph nodes, blood, testes (Hueper, Wiley and Wolfe)), which in turn may give rise to an increase in the urinary excretion of the aforementioned acids, unrelated to that caused by detoxification of the aromatic amines. It appears also likely that there are other conversion products contained in the urine in addition to the one mentioned.

Recent investigations of Wiley have shown that only a part of the beta-naphthylamine administered to dogs could be accounted for by the 2.1-

aminonaphthol ether sulfate isolated from the urine. Wiley suggested that possibly other portions of the aromatic amine might be eliminated in conjugation with mercapturic acid. The carcinogenic azo-dyes seem to undergo a different type of metabolic degradation. Ortho-amino-azo-toluene first is reduced in part in the azo-position to p-toluylenediamine, which is excreted after acetylization as diacetyl-p-toluylenediamine (Hashimoto). The experiments of Yamazaki and Sato, if confirmed, on the other hand, would indicate that the aromatic amine (intermediate) as well as the azo-dye are capable of eliciting neoplastic responses by a direct action upon the bladder mucosa.

Mayer suggested that possibly hypersensitivity is involved in the causation of aniline tumors. In support of this hypothesis he pointed out that some of the related aromatic amines (para-phenylenediamine and other ursol compounds) are responsible for the frequent occurrence of occupational dermatitis, asthma and rhinitis on an allergic basis among fur dyers. The supposition is that some of the conversion products formed in the body from the carcinogenic aromatic amines are chemically highly reactive quinogenic substances which can combine easily with protein complexes and thus form chemospecific antigens. Hueper (1936), and Hueper, Briggs and Wolfe have dealt recently with this aspect of the causative mechanism of aniline tumors in two communications which discuss the chemo-immunologic and histologic evidence which seems to favor such a conception (Landsteiner; Marrack; Klopstock and Selter; Boyland and Warren; Creech and Franks; Reuterwall; and others). Attention may also be called to a paper of T. Bauer on the serum antibodies against various endocrine and other organic substances containing phenol groups, as the antibodies produced showed chemospecific qualities in the presence of the phenol group and thereby demonstrated the possibility that similar systemic immune reactions may follow the introduction of aromatic amines.

According to the present conceptions of the causative mechanism of allergy, it appears necessary to assume that these chemicals first combine in the body with proteins, thereby forming antigens, of which the aromatic amine is the hapten, before histogenic sensitization can occur. The investigations on the chemical constitutional specificity of immune bodies by Landsteiner and coworkers, Klopstock and Selter, Marrack, and others, have thrown some light on the chemical structure and biologic qualities of such compounds.

Landsteiner succeeded, by diazotization of various aromatic amines (aniline, etc.) and by coupling the resulting diazo product with protein, forming "azo-proteins", in obtaining substances capable of antibody production of specific nature. Precipitin and complement fixation reactions performed with these azo-proteins and their antisera proved to be specific for the aromatic group, while the protein component had lost its species specificity through the coupling process and did not react. It was therefore possible to use homologous protein in the preparation of the azo-protein and still obtain an antiserum.

The experiments of Pauly indicated that the coupling of the diazo compounds takes place at the tyrosin and histidin groups of the protein molecule. Landsteiner suspected that the coupling takes the form of a quinoid structure of the substituted aromatic rings (Suida; Mayer).

The formation of quinoid structures is of interest in this connection for several reasons. It appears probable that the formation of allergens by non-diazotized amines in the organism may be explained by the fact that they are there converted into quinone substances which will couple rather easily with protein (Suida; Mayer). The $-NH_2$ and $=NH$ groups of the amino acids react with the CO group of the quinone, forming compounds of a quinoneanilid-like character, besides other still unknown combinations, of which a binding to the free —SH group may be one, since these are easily included in the coupling. The union of the quinone with the protein causes changes in the latter from its original solubility and precipitability, indicating that the protein molecule undergoes a fundamental chemical transformation (Ellinger) which is probably of significance in regard to the immunologic properties of the quino-protein compounds. Quinone substances are known for their marked tendency to cause allergic disorders of various types. Mayer claimed that only those aromatic amines which have quinogenic qualities and therefore can couple with protein are capable of acting as stimulants for epithelial proliferation. Stoltzenberg asserted that the quinone bodies combine with the protein of the cell nuclei. After the subcutaneous introduction of various quinone-forming aromatic amines, such as naphthylamine, para-phenylenediamine, p-xylidine, and other diamines and para-phenols, he observed black clumps in and around the cells of the basal layer of the epidermis sometimes filling the entire cell. The clumps were irregularly distributed among the cells in the basal layer and seemed to form occasionally bead-chain-like networks surrounding the cells.

With these immunologic-chemical observations as a proper background for a clearer understanding of the causative mechanism active in the production of allergic reactions resulting from exposure to aromatic amines, it is important to note that quinone bodies and generators have been demonstrated in the urine as organic conversion products of substances (aniline, naphthylamine, benzidine) evidently involved in the development of "aniline tumors" of the bladder.

The organic conversion products of aniline are mainly phenylhydroxylamine, which, after spontaneous oxidation to azoxybenzol, is eliminated as such, and para-amino-phenol, which is a quinone former and changes spontaneously and readily into quinonimine. This is in turn reconverted under formation of methemoglobin into quinone (Heubner). Engel who studied the metabolism of beta-naphthylamine, recovered from the urine of treated animals 2-amino-1-naphthol which has the ability to form quinonimines (Heubner), and dihydroxynaphthylamine (hydronaphthoquinone). Will-

staetter and Kalb pointed out that benzidine is converted by the action of oxidizing agents into an unstable di-pheno-quinonedimine. With this evidence available, the fundamental requirement for the production of allergic reactions in the bladder of persons exposed to these substances appears to be met.

Allergic conditions of the urinary tract are clinically characterized by attacks of tenesmus, involuntary emptying of the bladder, pain, hematuria, urinary eosinophilia, and enuresis (Duke; Piness and Miller; Kämmerer; Westphal; Nicholas). They are attributed to the reaction of the leiomyo-vesical tissue to the allergen. The information in the literature on bladder allergy is scanty. This must appear unusual in view that antigens are quite frequently excreted with urine. Recent experiments of Guerrisi have demonstrated that the bladder can be sensitized and will react against the sensitinogen with symptoms, such as seen in the Arthus phenomenon. Investigations of Akaeda have shown, moreover, that rabbits can be sensitized against heterogeneous erythrocytes introduced repeatedly into the lumen of the bladder. Akaeda interpreted this unusual observation as evidence that protein matter can be resorbed into and through the bladder-wall similar to the resorption of drugs of various types.

Attention may be called in this connection to the observation of vestibulo-urethral conditions with cystalgia usually found in women of advanced age, caused by the presence of intraureteral papillomas and polyps (Albano). These are composed of an edematous, highly vascular connective tissue infiltrated with neutrophilic and eosinophilic leucocytes and lymphocytes and thus resembling, in their general morphology, the nasal polyps of allergic origin, as well as the vesical papillomas. In addition to their pseudoangiomatous structure, fresh hemorrhages and old blood pigment frequently are found in these formations, which are reaction products in a mucous membrane penetrated readily by a great variety of organic substances (Macht).

While it is known that severe urinary symptoms, such as polyuria, dysuria, tenesmus, pain, or hematuria are characteristic of acute poisoning by these above mentioned aromatic amines, the data on the frequency, duration and type of urinary symptoms contained in communications on aniline tumors suggest the possibility that similar attacks, preceding the appearance of tumors, observed in dye workers in the absence of any symptoms of poisoning, apparently are of an allergic nature (Anderson; Simon; Engel).

The amounts of aromatic amines which the workers may resorb by any route in a day are, in general, so small that actual poisoning does not take place. This conception is supported by the clinical observations made routinely at cystoscopic examination of dye workers. Local areas of congestion, edema, hemorrhage and of telangiectatic, pseudoangiomatous lesions of transitory character are not infrequently observed at the cystoscopic examination of these laborers (Simon; Anderson; Gay; Hueper; Ferguson). Hueper has called attention to the occurrence of highly edematous, and vascular vesical polyps

which often contain intra- and extracellular eosinophilic infiltrations, hemorrhages, angiectases, and intravascular endothelial "thrombus-like" knobs; these resemble in many respects the nasal polyps of chronic and allergic rhinitis and display thus a certain likeness with the morphological manifestations characteristic of chronic allergic-hyperergic reactions.

The allergic-carcinogenic concept offers a plausible explanation for the variations in individual reactivity (predisposition: acquired and congenital) and thus for the varying length of latency or exposure time observed as well as for the frequent multiplicity of aniline tumors, and their site and extent in the bladder. The existence of a polyallergy to chemically related compounds makes it easier to understand that any one of a group of aromatic amines may start or continue a carcinogenic reaction in the vesical mucosa. Such chemospecific immunologic interrelations may indicate the manner by which normal or pathologic metabolites of similar chemical structure and of known growth stimulating quality (skatol, indol) may possibly continue an allergic-carcinogenic reaction initiated in the bladder by the exogenous chemical agents, and, thereby, may cause the development of vesical tumors many years after the cessation of occupational exposure to the aromatic amines.

Ullmann contended that aniline, as well as other hydrocarbons, exert an inhibiting effect upon the cellular ferments (catalase) which are supposed to prevent the unrestrained growth of cells (Bloch, Bristol). Present knowledge, in regard to the relation of intracellular enzymes to cellular growth activity, is by far too uncertain and controversial to consider this explanation as plausible. For instance, Wiley could not demonstrate any effect upon the respiratory index of rat tissue (liver, kidney) exposed to a solution containing beta-naphthylamine or removed from animals treated with this compound (Barcroft-Warburg method). Prolonged subcutaneous administration of beta-naphthylamine to dogs also had no significant effect upon the glucose, glutathione, calcium or phosphorus content and the pH of the blood (Wiley).

These investigations have not provided definite information as to the exact nature of the carcinogenic agent nor the mechanism of its action on the cells of the bladder mucosa. It remains doubtful whether these substances are directly or indirectly carcinogenic, i.e., whether they elicit a neoplastic response in a predisposed tissue or produce a conditioning of the mucosa so that other substances may induce the tumorous response (Latzko). In reference to these considerations, Scheele (1926) pointed out that, in general, substances which produce a cancerous predisposition are also carcinogenic (tar).

There may be mentioned in this connection a proposal made by Stallybrass, who suggested an investigation of the combined action of amino bases and arsenic in the production of bladder tumors on the assumption that the effects of the two substances may be synergistic. Such an experiment appears to be appropriate in view that prolonged ingestion of small amounts of arsenic

on vegetables and fruits is not uncommon since the introduction of arsenic-containing sprays as insecticides.

Kuchenbecker devised a qualitative test for the demonstration of aromatic bases in the urine of persons exposed to these compounds. By diazotizing these substances in the urine and coupling the resulting products to the sodium salt of a phenyl or benzoyl derivative of 2,5,7-aminonaphthol sulfonic acid, a reddish compound is obtained. Kuchenbecker claimed for his test also quantitative effects, but Berenblum commented that the test is good only for qualitative results and is unreliable in quantitative respects. Kuchenbecker found the largest amounts of aromatic amines in the urine of workers exposed to inhalation of substances in dust form.

VI. TIME OF EXPOSURE AND PERIOD OF LATENCY

In conformity with observations made on occupational tumors in general, aniline tumors will ensue, as a rule, only after a relatively long time of exposure to the carcinogenic agents. Although no definite information exists concerning the minimal time necessary for eliciting a blastomatous change, various authors place the minimal period in general at two years. Koelsch, however, contended that an exposure of only six months to beta-naphthylamine may be sufficient to cause a neoplasm of the bladder.

Oppenheimer (1927) recorded that the period of exposure ranged from one to forty-one years, with an average of seventeen years, while the first symptoms were observed from eight to forty-one years of exposure, with an average of eighteen and a half years. Mueller's (1936) observations are similar (exposure period, from two to twenty-eight years; first clinical symptoms, from nine to twenty-eight years, with an average of eighteen years). Henschen gave the average length of exposure as seventeen years (range, from two to thirty-five years); the average time of exposure for benign tumors in his experience was fourteen years and four months and that for malignant neoplasms nineteen years. Gehrmann found, on the other hand, that the average time of exposure for 24 malignant tumors was 13.2 years, and for 39 benign tumors 12.07 years.

In a series of 137 cases collected by the author from the European literature, the incidence of tumors after various periods of exposure appears as follows:

Years	*1-5*	*6-10*	*11-15*	*16-20*	*21-25*	*26-30*	*31-35*	*36-40*
Cases	16	20	29	35	16	9	6	6

Evans arranged his 83 American cases according to duration of exposure as follows:

Years	*1-5*	*6-10*	*11-15*	*16-20*	*21-25*	*26-30*	*31-35*	*36-40*
Cases	11	20	28	21	2	1	0	0

A comparison of the two tabulations reveals the fact that, in the American

series of Evans, 71 per cent of the tumors appeared within from one to fifteen years after exposure, while in the European series of Hueper only 47 per cent developed within the same time of contact. Whether or not this indicates differences in degree of exposure remains at present a problem for research. Attention may be called, however, to the fact that in the majority of the American cases the exposure was to beta-naphthylamine, which, according to Engel (1937), is apt to cause a neoplastic response more quickly than the other aromatic amines.

A characteristic feature of aniline tumors which is of great medical, medico-legal and social importance is that they may develop many years after exposure to the carcinogenic agents has ceased. Nassauer reported that in some of his cases tumors appeared from one to seventeen years (average eight years) after the termination of the hazardous work. This phenomenon is not unique, as similar observations have been made regarding the time of manifestation of carcinoma due to arsenic, tar, soot and roentgen-rays. A reliable explanation of this peculiar behavior is, however, still missing. It may be assumed that the exposure produces at the time a conditioning of certain cells or cell complexes in the wall of the bladder which may make them especially sensitive to normal or abnormal stimuli of growth. Whenever this cell-fixed quality can exert itself, owing to lack of normal growth-restraining influences or to an excess of agents promoting proliferation, tumor formation will result, similar to the sudden manifestation of a chemical hypersensitivity following many years of apparently harmless contact.

The length of exposure has been related to the biologic characteristics of the ensuing tumors (Henschen). It was assumed that the neoplasms were primarily benign and were transformed subsequently into malignant growths as contact continued with the carcinogenic substances. This was soon recognized as incorrect, for it was observed that malignant tumors may develop as early as benign ones (Oppenheimer, 1926, Curschmann). This conception is confirmed by Hueper's (1934) compilation of 93 instances recorded in the literature:

Years	*1-5*	*6-10*	*11-15*	*16-20*	*21-25*	*26-30*	*31-35*	*36-40*
Benign tumors	2	0	2	4	4	2	0	0
Malignant tumors	8	13	16	24	8	5	2	3

Furthermore, histological observations in sections from the bladders of dogs with aniline tumors furnished definite proof that many of these neoplasms are malignant from the start and do not pass through a benign stage (Hueper, Wiley and Wolfe).

VII. CHEMICAL CHARACTER OF COMPOUNDS AND NEOPLASTIC RESPONSE

Engel (1937) stated that of the three aromatic amines (aniline, benzidine, beta-naphthylamine) beta-naphthylamine appeared to be the most carcinogenic,

as it seemed to produce bladder tumors most rapidly and most frequently. In support of his contention, he presented the following tabulation:

	Aniline and Homologues	*Benzidine*	*Beta-naphthylamine*	*Other Bases*
Cases	78	25	67	19

Similar relations are apparent from the tabulation published by Evans:

	Benzidine	*Beta-naphthyl-amine*	*Alpha-naphthyl-amine*	*Miscel-laneous Aromatic Amines*	*Alpha- and Beta-naphthyl-amine*
Cases	13	16	20	27	7

The high incidence of bladder tumors following exposure to beta-naphthylamine is shown by the absolute number listed. It becomes more striking if consideration is given to the fact that in Germany many more men are employed in operations employing aniline than in operations employing beta-naphthylamine and that there are 29 additional cases on record in that country in connection with which beta-naphthylamine exposure is highly probable (Engel, 1937).

While Berenblum conceded that there are differences in the tumor incidence in the different departments of a dye factory, he noted at the same time that there is no reason to believe that the morphology of the tumors observed in the different departments varies and depends upon the particular chemical handled. Engel (1937) is, on the other hand, of the opinion that the benign or malignant character of a bladder lesion has a certain relation to the chemical nature of the aromatic amine which caused it. Tumors resulting from exposure to beta-naphthylamine are, according to his contention, more likely to be papillomas, while those following contact with aniline, benzidine and their homologues are more frequently primarily malignant. He offered the following compilation in support of his claim:

	Aniline and Homologues	*Benzidine*	*Beta-naphthyl-amine*	*Other Bases*
Cases of papillomatosis	11	5	16	5
Cases of carcinomatosis	25	22	15	5

Di Maio contends that beta-naphthylamine seemed to transform papillomas more rapidly into carcinomas than benzidine.

An analysis of the data furnished by Gay in regard to the American cases seems to support, to a certain degree, the opinion of Engel (1937). Among 59 bladder tumors diagnosed histologically, 29 were malignant and 30 were benign; that is about the same ratio as found by Engel for the beta-naphthylamine tumors. As the majority of the American patients had been exposed

to beta-naphthylamine and considering that most of their lesions were relatively early, some support can be given to Engel from this source.

It has been asserted that bladder tumors, having their genesis in exposure to aromatic amines, appear in an earlier period of life than those of unknown cause. Schär stated that aniline tumors are especially frequent in men between 30 and 40 years of age. Büttner found that the average age of the afflicted workmen was 48, the youngest being 38 and the oldest 54. Oppenheimer (1927), on the other hand, noted that malignant tumors are not frequent in men between 30 and 40 years of age. The fifth decade was, according to him, the period during which the majority of aniline tumors were seen. The 94 instances collected from the European literature by Hueper (1934) were distributed in the various age periods as follows:

Years	*20-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*Total*
Hueper's series of European cases	3	21	40	52	11			127
Evans' series of American cases	5	19	23	29	6	1		83
Joseph's series of cases of unknown origin		13	32	46	41	21	4	157
Wilinski's series of cases of unknown origin	2	8	27	39	22	4		102

The combined aniline tumor series show 52.4 per cent of the cases before the fiftieth year, while the two cryptogenetic series have only 28.6 per cent in the same age range. The evident shift toward the younger age groups contradicts the statement of Engel that the aniline tumors are rarely seen before the fiftieth year. He concedes, however, that they may occur at an earlier age provided the individual is exposed to very active carcinogenic substances, such as beta-naphthylamine. The American series, with its high proportion of cases exposed to this compound mentioned, apparently confirms this part of Engel's contention, as it shows the most marked shift toward the younger decades of life. A definite decision in this matter depends upon a proper consideration of the average age at which the occupational exposure starts for the dye worker in Europe and in the United States. In view of the fact that many of the workers in dye factories entered employment at a rather early age, the foregoing observations present important support for the conception that not the age but the duration of exposure is the determining factor in the development of aniline tumors (Curschmann; International Labour Office; Kennaway).

On the other hand, age, inasmuch as it goes parallel with duration of exposure, may have some relation to the biologic character of the aniline tumors observed. It appears that with increase in age there is a corresponding

appreciable increase in the proportion of the malignant neoplasms, as is evident from the following evaluation of 62 instances collected from the European literature:

Years	*20-30*	*31-40*	*41-50*	*51-60*	*61-70*
Benign tumors	1	2	3	2	0
Malignant tumors	0	6	22	29	7

As the European tumor of this type usually is not discovered during an early developmental stage, these figures suggest the possibility that some of the benign tumors undergo malignant transformation at some point in their course and thereby increase the proportion of malignant tumors in the older age groups.

VIII. SYMPTOMATOLOGY

As aromatic amines are hemotoxins (methemoglobin formers), acute anilism is characterized by cyanosis, usually associated with stranguria, hematuria and symptoms of transient cystitis (Bachfeld). Rossbach, who in 1885 recommended naphthylamine as an intestinal antiseptic, recorded similar symptoms in patients who were subjected to this medication. Engel (1920 and 1924) observed these manifestations in dogs acutely poisoned with beta-naphthylamine. Such attacks are known to have occurred only rarely as a result of exposure to this substance during its production and handling (Engel, 1937). Apparently, acutely toxic doses are thereby rarely introduced (Mueller, 1936), as so far only two cases of acute hemorrhagic cystitis, following massive inhalation of beta-naphthylamine dust, have been placed on record. As frequently there have been no acute attacks of cyanosis and urinary symptoms in the lives of persons afflicted with aniline tumors, it is highly doubtful, whether such occupational episodes are of diagnostic or causative significance. In only 13.5 per cent of Anderson's 23 cases did the patient give a history of urinary disturbances preceding the discovery of the tumor. Washburn reported that 52 per cent of the patients showed no symptomatic evidence of tumor of the bladder. Wolfe related that only 4 of 65 patients had hematuria, urgency and frequency of urination and that all 4 had well advanced tumors. Only a few of the remaining patients showed occasional red blood cells in the urine.

Aniline tumors, therefore, do not produce during their early developmental stages any subjective symptoms, and these may be absent even when the neoplasms are well advanced. Hematuria, intermittent or constant, is the most frequent early symptom. Other subjective complaints more or less often noted during later stages of the disease are stranguria, burning sensation at urination, pain in region of the bladder, frequent micturition, oliguria, difficulty in urination and the passing of shreds. For a long time the symptoms remain purely local, and the general health is not affected seriously. The urine is usually sterile on culture (Oppenheimer).

These observations show convincingly that the only reliable and effective

means of early discovery is offered by periodic cystoscopic examinations of the persons exposed (Oppenheimer, 1926; Gehrmann; Baader). Unfortunately, such a procedure frequently meets with resistance by workers (Wolfe). For this reason in German and Swiss plants cystoscopic examinations are not done as a routine, but only when hematuria has been demonstrated repeatedly. Urinalyses are there performed at intervals as a routine. A similar practice is observed in English plants (Bridge).

Engel (1937) stated that cystoscopic examination may show *three morphologic types of lesions of the bladder in chronic poisoning with aromatic amines:*

1. *Lesions due to chemical irritation of the bladder.* The bladder presents hemorrhagic spots, situated mainly in the trigonal space and around the ureteral and urethral orifices. This reaction usually recedes within two to three weeks. Months or years later tumors may be observed rarely in the same areas in which the hemorrhages occurred.

Wolfe observed these "submucosal hemorrhages" of varying size and extent in some of his patients, especially during the summer months, and commented that on subsequent cystoscopic examinations the hemorrhages had disappeared, leaving the bladders of these patients clear and normal. Reference to the presence of such hemorrhagic spots in the mucosa of the bladder of the dye worker was first made by Simon (1932), who observed the development of tumors at the sites of these spots several years later. Gay and di Maio (1937) described them as hyperemic spots, resulting from capillary hyperemia and telangiectases (spider vessels). They were usually located in the lower half of the bladder, where the convolutes of dilated vessels caused slight local elevations of the overlying epithelium. While Simon, di Maio and Ferguson asserted that these lesions are precursors of tumors and that thereby the future occurrence and location of bladder neoplasms can be predicted, Engel (1937); Berenblum; and Hueper, Wiley and Wolfe concluded that they are not of precancerous character but represent transient acute vascular reactions of the vesical mucosa.

2. *Benign papillomas.* These may be polypous or villous, pedunculated or sessile, and are often multiple. They are most often located in the trigonal and paratrigonal region, especially around the ureteral orifices, conforming in this respect to the cryptogenetic tumors (Hueckel; Matthews).

3. *Carcinomas.* These are usually broad-based papillary tumors, but nodular infiltrative neoplasms also occur. They are situated, according to Engel (1937), with equal frequence in all parts of the bladder, unless they develop from primary papillomas. In the latter case they are most often found near the ureteral orifices and in the anterior and posterior walls, as well as near the urethral orifice. The tumors are rarely located in the renal pelvis or in the posterior part of the urethra (Oppenheimer).

Similar lesions were seen cystoscopically in the bladders of dogs exposed to subcutaneous and oral administrations of large amounts of commercial

beta-naphthylamine (Hueper, Wiley and Wolfe), and may be divided according to their appearance and character into three groups:

1. *Transient inflammatory and vascular reactions.* The most frequent and earliest pathological manifestations were represented by well defined "hemorrhagic spots." As a rule these consisted of localized convolutes of engorged capillaries, to which, occasionally, highly hyperemic and tortuous larger vessels extended in radiating formation. In other instances the red stipplings were definitely hemorrhagic extravasations. Multiplicity and group formation were a striking characteristic of these lesions. Areas of bullous edema were rarely seen. In a few instances there were also small sloughing mucosal ulcers. The mucosal hemorrhagic spots were frequently of highly transient nature and disappeared without leaving a trace, so that it appears improbable that these vascular manifestations represent precancerous lesions.

2. *Localized mucosal thickenings.* These were well circumscribed orange to brown-red or blanched areas, with or without elevation, occasionally showing tiny raised points, which on subsequent examinations often definitely had the appearance of early papillomas. The surfaces of these foci were sometimes rough and bled easily. Spontaneous regression of this type of lesion was observed repeatedly, but more frequently there occurred progressive development into a tissue response that was definitely neoplastic. In contradistinction to this, tumors also appeared in areas which had not shown evidence of preceding mucosal abnormality.

3. *Tumors.* The neoplastic proliferations were usually of a papillomatous type. Many were pedunculated; others were sessile and of broad base. Many of the early lesions had the appearance of small edematous mucosal polyps. The well developed papillomatous growths were, in general, composed of rather plump villi, sometimes showing hemorrhagic tips or sloughing lesions. Delicate, feathery papillomas were uncommon. Infiltrative nodular tumors were observed in several instances. Neoplastic multiplicity was the rule, often attaining the status of general papillomatosis.

In contrast to the human tumors with their most frequent site on the floor of the bladder, the canine neoplasms were found most often in the region of the dome and the adjacent parts of the anterior and lateral walls. Tumors located on the proximal portion of the posterior wall and on the floor of the viscus were relatively rare and usually coexisted with general papillomatosis.

The incidence of pathologic lesions of the bladder increased, according to the observations of Hueper, Wiley and Wolfe, with the duration of exposure, not only in the entire series of 16 dogs but also in the individual animal. There was at the same time an increasing frequency of definitely neoplastic lesions.

IX. HISTOLOGY

In structure the lesions occurring in the bladders of workers exposed to aromatic amines vary greatly. Some are purely or mainly of inflammatory type;

others present epithelial hyperplasia as their most prominent morphological feature, being identified thereby as precancerous; while a third group is definitely neoplastic. Whereas a reasonable amount of information has existed for some time concerning the histologic structure of the tumorous formations, little was known for many years in regard to the other two types of lesions mentioned. It is only in recent years, through several observations of Rössle and Teutschlaender and the work of Gay and Ferguson, that histological data became available concerning some of the moderately early changes occurring in the submucosa and mucosa of the bladder of the dye workers. The two last-mentioned authors rendered the following description of these lesions, from which they drew certain conclusions in regard to the formative mechanism of aniline tumors.

The terminal capillaries in the mucosa become dilated and surrounded by lymphocytes. The vessels resemble miniature varices and are composed of thin-walled spaces, lined with endothelium but lacking in smooth muscle. Somewhere in the vicinity there is usually a vessel showing concentric proliferation of the endothelium. The lumen of such a vessel consequently is narrowed or occluded, and this plausibly explains the dilatation of its afferent capillaries. Increased intracapillary pressure plus continued action of the toxic agent may then result in further endothelial proliferation with the formation of new vascular spaces. The occluding mass of endothelium is gradually replaced with connective tissue, which becomes hyalinized. A natural result of the congestion is exudation. Edema and a few cells from the blood are frequently to be seen in the surrounding tissue. The presence of numerous lymphocytes and occasional eosinophils in the subepithelial tissue suggests chronic irritation. In the early lesions the epithelium and connective tissue are inactive. Ferguson assumed that the next step is fibrosis and the growth of new capillaries beneath the basement membrane of the mucosa, followed by rapid multiplication of the basal epithelial cells of the mucosa. The hyperplasia of these cells plus the activity of the submucosa causes the mucosa to become raised and at a later stage to form papillary projections, subsequent to which the neoplastic basal cells break through the superficial layers with resultant formation of a typical papillary carcinoma. Gay, on the other hand, noted that the vascular lesion may disappear and the area remain normal or there may appear at this site later on an epithelial tumor. The latter event is characterized microscopically by a variety of changes. The cells may become vacuolated. Small cysts are formed, and there may be cystitis cystica. Often the epithelium is atrophied locally. The earliest neoplastic lesion consists of a proliferation of the basement layer of the epithelium in the form of a simple projection of the vesical epithelium with a mass of blood vessels extending into it from its base. In other instances the proliferation shows a downgrowth, which may extend under the adjacent normal epithelium.

The histological structure of the aniline tumors is stated to be identical

anatomically with that observed in bladder tumors of unknown cause. More detailed information as to the different types and their relative frequency is not readily obtainable from the descriptions in individual case reports. Gay has grouped his 61 cases, according to the grade of histologic malignancy, as follows:

	Gay's Aniline Series		*Gaylor's Cryptogenetic Series: 480 Cases*
	Cases	*Per Cent*	*Per Cent*
Early lesion	2		
Papilloma, grade 1	30	55.66	10
Papillary carcinoma, grade 2	14	26.00	32
Carcinoma, grade 3	9	16.00	35
Carcinoma, grade 4	1	2.34	23
Carcinoma, ungraded	2		
Mixed grades	3		

The marked discrepancy in the distribution of grades in the two series is due to the fact that the occupational tumors come to observation at a stage before some of them have undergone malignant transformation.

Among them were tumors with squamous and adenoid features but none was of sarcomatous type.

The author had the opportunity to examine and evaluate biopsy sections obtained from bladder lesions found in 67 dye workers (125 specimens, 25 of which represented early lesions, such as inflammatory reactions, mucous polyps, polyps with papillary epithelium and leukoplakia) and similar sections removed from 14 dogs which had been exposed to commercial beta-naphthylamine and had acquired bladder tumors (85 biopsy specimens). In addition, the author has studied numerous sections prepared from the bladders of 5 of these dogs which came to autopsy. Four showed grossly diffuse papillomatosis. One had remained cystoscopically normal. As neither a detailed nor a systematic presentation of the histologic character of preneoplastic and neoplastic lesions of the bladder caused by aromatic amines has been rendered, the following description, based on the evidence mentioned and representing a composite picture of the various changes seen in man and dogs, is given.

Non-neoplastic Lesions.—The non-neoplastic lesions of the bladder can be divided into the following types:

1. Inflammatory reactions (simple and ulcerative, i.e., irritation bladder and aniline ulcer (Henschen)).
2. Intra-epithelial abnormalities.
3. Leukoplakia (simple, papillary and infiltrative) (Müller, A. (1931)).
4. Mucous polyps (simple, papillary and infiltrative).

1. *Inflammatory reactions of chronic type.* These were observed occasionally in man and dogs. Such a lesion appeared cystoscopically as a small reddish

edematous elevation, sometimes surrounding a small mucosal defect or assuming the shape of a short polypous or warty protrusion.

The epithelial lining over the lesion was often atrophic, i.e., it consisted of two or three layers of small pyknotic and vesicular epithelial cells. Epithelial defects were not rare, especially in the polypous manifestations. The defects were filled either with chronic inflammatory granulation tissue or presented a bare connective tissue surface. A thickened epithelium was present in a few instances. The subepithelial connective tissue was always more or less edematous. In several lesions this condition reached such a degree that the epithelial lining was lifted from its supporting tissue and an ill defined serous subepithelial blister formed (bullous edema). The stroma, especially beneath the mucosa and around blood vessels, was usually mildly to moderately infiltrated by lymphocytes with, not infrequently, an appreciable admixture of eosinophils. Loose esosinophilic accumulations occasionally filled the subepithelial capillaries. The vascular network in the submucosa often was dilated and denser than normal, while varicose and ectatic capillaries were found, commonly, in the polypous formations. Only rarely were knoblike endothelial proliferations present and, when present, were in general associated with, or were contained within, small edematous polypous protrusions.

The endothelial granulomas which were found attached to the walls of precapillary, and occasionally also to ectatic capillary vessels, varied somewhat in appearance, depending on the age of the lesions and their size. In some vessels the endothelial lining showed localized endothelial proliferations, consisting of small clumps of swollen endothelial cells projecting like small polyps into the vascular lumens. With increasing size and age, these knoblike protrusions became less cellular and more hyalinized, ultimately causing complete occlusion of the affected vessels. The walls of such vessels were sometimes thickened by concentric layers of endothelial cells. There was in general no perivascular lymphoid accumulation connected with this type of endothelial obliterative angiitis. On the other hand, perivascular fibrosis and hyalinization were frequently associated with it.

Large focal lymphoid accumulations, occasionally containing centers of paler stained large cells, were characteristic of the inflammatory condition in some instances. These lymph follicle-like formations, which were located either directly beneath the epithelial lining, sometimes penetrating and replacing it, or formed the centers of larger edematous protrusions, were surrounded by loose connective tissue, often containing eosinophilic cells and old blood pigment. This peculiar type of lymphoid manifestation was the only morphologic response demonstrable in repeated biopsy sections removed from a dog, which even after thirty-two months of treatment with beta-naphthylamine, did not show any neoplastic lesions. Similar lymphoid tissue reactions (cystitis follicularis) were observed in several biopsy specimens obtained from dye workers. Whether this particular type of morphological reaction in the

bladder is indicative of a special type of biologic response cannot be decided from the evidence available.

It can be stated, however, that inflammatory manifestations evidently play no important or essential part as precursors of the development of neoplastic conditions. Their occurrence must be attributed to the presence of cytotoxic substances in the urine which, when resorbed, elicit the inflammatory chemotoxic response.

2. *Intra-epithelial abnormalities.* Localized pathological changes in the morphologic character and arrangement of the epithelial cells in the mucosa of the bladder so far have not been observed in man, apparently because of technical difficulties. They are, however, frequently observed in the bladders of dogs exposed to beta-naphthylamine and are considered as the earliest pretumorous response of the mucosa to the carcinogenic agent.

In such lesions the epithelial lining is thinned, in many instances consisting of small pyknotic cells, ill defined, closely packed, irregularly arranged and occasionally forming indistinctly outlined intra-epithelial nodules. In other instances it is composed of cells with vesicular cytoplasm and small hyperchromatic nuclei. The irregularity of the cells in size, shape, arrangement and stainability is so marked sometimes that the lesion has the appearance of a noninfiltrative carcinomatous coating, similar to that observed in the human uterine cervix. There are also areas made up of small, indistinctly contoured, hyperchromatic cells arranged in numerous short pointed or tongue-like, solid epithelial papillae. The basal line of the epithelium, in all of the conditions just described, is sharp and straight. There are no vascular or connective tissue changes in the submucosa. In some instances small intraepithelial nodules have separated partially from the epithelial lining and seem to drop off into the submucosa.

3. *Leukoplakia.* The mucosa consists of a markedly thickened epithelium, composed in the deeper layers of transitional cells and in the more superficial layers of large polygonal cells. The cells are usually irregular in shape and size and often swollen, vesicular or balloon-like. Small intraepithelial cysts, apparently resulting from localized liquefaction necrosis within the epithelial mucosa and filled with a bluish or pink-staining homogeneous matter, often are found. In some of these lesions, the epithelium is arranged in short, indistinctly demarcated, plump, solid epithelial papillae. Rounded or pointed epithelial pegs, usually, but not always distinctly outlined, and extending into the sub-epithelial connective tissue, are a characteristic feature. In some instances the loss of polarity is complete. Large, ill-defined round or polygonal epithelial cells infiltrate beneath the mucosal lesion in small groups and strands or as individual cells, penetrating the submucosa and producing the picture of a minute anaplastic carcinoma. The epithelial changes described resemble in many respects those seen in the skin as morphologic expressions of precancerous roentgen-ray and arsenical dermatosis.

The subepithelial connective tissue is usually edematous and infiltrated with lymphocytes and leukocytes, which are at times predominantly eosinophilic. Brown-pigmented phagocytes occur in some instances in larger number in the connective tissue directly beneath the epithelial mucosa. The capillaries often are dilated and hyperemic in the more advanced lesions, which show also an increased density of the capillary bed. Newly formed capillaries extend sometimes from the submucosa through a highly edematous subepithelial zone into an indistinctly outlined and irregularly arranged mucosa. Their content of eosinophilic cells is remarkable. Endothelial granulomas are found in about 50 per cent of these leukoplakic lesions. Some of the most advanced, and even early malignant changes of this type, are not accompanied by inflammatory or vascular reactions of the submucosa. In those instances the epithelial cells invade diffusely an apparently normal submucosa.

4. *Mucous polyps.* The small knoblike mucosal protrusions with narrow pedicles, found in the bladders of dye workers and dogs exposed to aromatic amines, show many of the histologic features just described. The epithelial lining of some of these mucosal polyps is composed of an atrophic, thinned pyknotic or vesicular epithelium, occasionally containing small defects filled by chronic inflammatory granulation tissue or presenting a bare connective tissue surface. In other instances the epithelium consists of from several to many layers of swollen, round-shaped vesicular epithelial cells with pyknotic nuclei. Multinucleated large cells and huge cells with giant-sized hyperchromatic nuclei are scattered sometimes in the hyperplastic mucosa, especially near the tips of the polyps. Markedly thickened portions of the epithelium contain also, at times, epithelial nodules and pseudo-glandular cysts. A number of these polyps show small solid epithelial or fibroepithelial papillary projections extending from the surface, while others show epithelial pegs and processes invading the submucosa. The latter processes are in some instances highly infiltrative and markedly atypical in cellular character, suggesting an early stage of anaplastic malignant change. These malignant transformations usually involve the tips of the polyps.

The stroma consists of an edematous, loose and, in general, very vascular connective tissue, often infiltrated with lymphocytes and eosinophilic cells. These are not infrequently the main cellular type found in the lumens of newly formed capillaries. The capillary vessels are usually ectatic and varicose. In two thirds of the polyps endothelial granulomas are observed within vessels located in the center or in the pedicle. Vascular changes often coexist with locally corresponding atrophic alterations in the surface epithelium. In many cases strands of smooth muscle tissue extend through the pedicles into the cores of the polyps and form there occasionally whirl-like, often hyalinized tufts.

The histological observations recorded concerning the precancerous lesions (intraepithelial abnormalities, leukoplakias, mucous polyps) demonstrate

clearly that the first preparatory cellular response to the contact with carcinogenic agents occurs in the epithelial lining of the bladder. These epithelial changes, occasionally, may advance even as far as an early infiltrative malignant lesion before any appreciable reaction of the surrounding vasculoconnective tissue is noticeable. It is this type of lesion which may escape cystoscopic discovery as it may not produce mucosal thickening or be associated with papillary projections or vascular reactions which would attract attention and provide visible evidence.

Chronic inflammatory, obliterative and ectatic vascular and fibrotic changes are apparently secondary and nonspecific. They are present in only part of the lesions and are often accompanied by atrophic epithelial alterations. The frequent formation of endothelial granulomas and the subsequent vascular obliteration may be attributed to three possible causes: 1) As they are found most often in polyps, it appears likely that the topographical distortion connected with the formation of the polyps may exert a twisting or stretching effect on the vessels and thereby elicit endothelial damage and proliferation. 2) Endothelial injury and regenerative proliferation also may result from the resorption of toxic products through the mucosa into the intraepithelial capillaries and thus angiectases may be caused. 3) There exists, moreover, the possibility that chemospecific allergic reactions are involved in the formation of endothelial granulomas, especially as many of the early lesions show intravascular and extravascular eosinophilia and marked interstitial edema (Hueper, 1936; Pagel; Reuterwall).

The frequency of vascular hyperemia and proliferation, which are observed in the great majority of precancerous reactions, suggests that an increase in the blood supply is an essential preparatory feature of neoplastic cell growth (Paschkis and Bruegel). This conception receives support from various sources. Ewing stated that increased vascularity has been demonstrated in the beginning of many carcinomas and has been assumed to account for the awakening of many cell rests. Thiessen found in his studies of the relative vascularity of benign and malignant gastric lesions that in an entirely unexpected and, as he felt, paradoxic way, the vascularity increased progressively from the simple ulcer to the ulcer with cytoplasia to the ulcer with early malignancy and decreased as the carcinoma became well established. Kreyberg concluded from his experimental investigations of the precancerous changes in the skin of tarred mice that marked local vascular hyperemia accompanies epithelial hyperplasia and, in association with other factors, may exert a stimulating effect on cellular proliferation. This conception is, moreover, in full agreement with well established experiences in regard to the nutritive influences controlling sustained cell growth (Hueper, 1933; Hueper and others, 1933). The observations made during the study of the early lesions of the bladder do not support, on the other hand, the belief that permanent vascular and circulatory insufficiency and fibrosis are the primary responses and that the neoplastic

proliferations develop on the basis of nonspecific abnormalities in the supporting connective tissue (Wolbach).

Neoplastic Lesions.—"Aniline tumors" may be grouped on pathological grounds under this classification:

1. Papilloma with histologically benign structure.
2. Papilloma with histologically benign and malignant component parts.
3. Carcinoma:
   (a) Papillary carcinoma of transitional cell type.
   (b) Nodular infiltrative carcinoma: transitional cell type; glandular type; anaplastic or sarcomatoid type.

1. *Histologically benign papilloma.* This type is represented by either villous tufts of varying size, composed of slender, delicate, feathery fibroepithelial projections, or by rather plump, thick, warty protrusions possessing a larger amount of usually edematous connective tissue between the epithelial covering. The papilloma may be connected with the wall of the bladder by a very narrow pedicle, or there may be a broader tissue bridge as connecting link; or numerous small papillary projections (papillomatosis) may extend from the mucosa of the bladder with narrow interspaces. The epithelial lining discloses marked variations in thickness and in cellular character. It may be represented by as little as two or three rows of cells or as many as twenty or more strata of epithelium. In the majority of cases, it closely resembles the normal transitional epithelium of the bladder. Occasionally papillomas are found which are covered by closely packed small oval or round hyperchromatic cells of an almost lymphoid character. Others occur which are lined by large polygonally shaped epithelial cells. Cells of this type may be seen, moreover, in the superficial layers of some of the transitional cell papillomas. Degenerative changes, such as balloon-like swelling, cytoplasmic vesiculation, nuclear pyknosis, atrophic shrinkage and intraepithelial cyst formation (pseudoglandular structures), are not uncommon features, especially in papillomas with thick epithelial lining. The merger of the epithelial covering of adjacent papillae may result in the production of broad solid epithelial sheets. The basal layer of the epithelium is always sharply demarcated from the connective tissue core, even in cases in which there is a moderate degree of irregularity in the morphology and arrangement of the epithelium.

The stroma is usually a loose, edematous and vascular connective tissue varying greatly in amount with the individual tumor. There is often a mild to moderate infiltration of lymphoid and mononuclear cells, containing not infrequently also a varying number of eosinophilic cells. Hemorrhages into the edematous tissue, especially into the tip portions, often are seen. There are, occasionally, phagocytic cells containing brown granular pigment in the neighborhood of vessels and directly underneath the epithelial lining. The interstitial edema may attain, in rare instances, such degrees that small central cysts filled with a pink-stained homogeneous matter are formed. These are

surrounded by a thin layer of connective tissue with a few capillaries, which in turn is covered by the epithelial lining. Tumors of this type have the appearance of a bunch of grapes.

There is present in general a rich capillary network. The vessels usually are dilated and hyperemic. The epithelial covering is not infrequently in direct contact with the endothelial lining. The capillary structures are sometimes so dense and dilated that the neoplasm has more the appearance of a papillary hemangioepithelioma. Degenerative changes in the vascular walls occur often. There may be hyaline thickening or calcium incrustation of the walls of these delicate vessels. Concentric endothelial thickening of precapillary vessels and endothelial granulomas, sometimes associated with fibrosis and hyalinization of the pedicle, are not uncommon.

2. *Papilloma with benign and malignant components.* This type exhibits a general pattern very similar to that just discussed. Side by side with the benign epithelium there occur, scattered throughout the epithelial coat, complexes of irregularly arranged and shaped cells, sometimes of large cellular and nuclear size. Mitotic figures are frequent and often irregular. Such foci may remain within the limits of the epithelial lining, or they may exhibit invasive properties, penetrating into the core and its vessels and through the pedicle into the base and underneath the adjacent mucosa. This development occurs more readily in papillomas, as the focal transformations with active malignant qualities are usually located near the base of the tumor, in contrast to those found in mucous polyps, in which they usually occupy the tip portions. The scattered distribution of these foci and the demonstrated transitional phases strongly suggest that papillomas with benign and malignant epithelial components are primarily benign neoplasms.

3. *Carcinoma:* (a) *Papillary carcinoma* is composed of rather bulky papillary projections lined by numerous layers of irregularly shaped and sized transitional epithelial cells. These cells, arranged in disorderly fashion, invade diffusely the loose and vascular connective tissue of the cores of the papillae and the bladder wall surrounding their base. Usually the tumor arises from a broad base, suggesting that papillary leukoplakia may represent the preceding condition. Normal and pathological mitoses are frequent in the epithelial strands. Giant cells with several nuclei, areas with polygonal cells and cornification, balloon-like swollen cells, pseudoglandular formations and other abnormalities may occur. The epithelial cells invading the connective tissue sometimes are arranged in garland formation. The structural characteristics of the stroma do not vary from those of the previously described type, but inflammatory reactions appear to be more frequent and pronounced in the frankly carcinomatous variety.

(b) *Nodular infiltrative carcinoma* originates either from a leukoplakic area or from epithelium showing merely atypical structure and arrangement of cells. In both instances epithelial cell strands and groups invade infiltratively

the submucosa, which often shows during more advanced stages a more or less dense lymphoid infiltration and increased vascularity. The tumor cells may vary markedly in type and arrangement. In the majority of tumors of this type, there is a definite resemblance to transitional epithelial cells. The cells grow in rather large, well circumscribed pegs. In other instances the cells are larger and paler staining and show a tendency to undergo liquefaction necrosis, thus producing pseudoglandular and pseudocystoglandular formations, which give the tumor an adenoid appearance. Spinous cell tumors are rare.

Neoplasms with true glandular structure are exceptional. They are usually composed of infiltratively growing tubules lined with high cuboid, low stratified hyperchromatic epithelium. More immature forms are still less frequent.

There occur also tumors of a completely undifferentiated type. The cells are round or oval and grow in large ill-defined masses, which are diffusely infiltrative. Tumors of this type have often a sarcomatoid appearance.

The malignant tumors occasionally observed in kidneys and renal pelves are of either papillary or large nodular structure and usually destroy large parts of the involved kidneys. They metastasize readily and are often very anaplastic.

Among the specimens obtained from human bladders, one of adenocarcinoma of the prostate gland and one of malignant dysontogenetic tumor of the floor of the bladder were included. While Oppenheimer (1926) considered the possibility that carcinoma of the prostate also might result from exposure to aromatic amines, Engel (1937) recently pointed out that such an assumption is unjustified, because carcinoma of the prostate is not more frequent among dye workers than in the general population. Statistical studies, made by Henry, Kennaway and Kennaway, on the death certificates of various groups of industrial workers with an excessive mortality from bladder cancer, showed that cancer of the prostate gland was not associated with these occupations, since only some of the groups had a high mortality rate from cancer of this organ, while others had a low one.

An occupational etiological relation of the dysontogenetic tumor could be construed only if activation of an embryonic tissue anlage by the occupational carcinogenic agent is assumed. This appears to be unlikely.

The histological examination of sections from human and canine tumors with special staining methods did not give any evidence in support of a virus etiology, as inclusion bodies in the tumor cells, especially those with the balloon-like distended cytoplasm, could not be demonstrated.

The various lesions described were distributed among the 125 human specimens studied in the following manner: chronic cystitis in 2; mucous polyps in 8; leukoplakia plus papilloma in 1; papilloma in 34; papilloma plus carcinoma in 10; papillary carcinoma in 23; solid, nodular carcinoma in 33; adenocarcinoma in 1; carcinoma of the renal pelvis in 1; dysontogenetic tumor in

1; prostatic carcinoma in 1. The histological grades of malignancy were recorded in 54 cases of carcinoma (cases of papilloma were not included, as this tumor was considered as histologically benign): Seven were of grade I, 23 of grade II, 19 of grade III, and 5 of grade IV. The low incidence of adenocarcinoma among aniline tumors agrees well with that generally found —2 per cent (Matthews), as well as with that found in Europe in aniline tumors (Seyberth recorded one case). Aniline tumors are, as evident from the observations in various countries, exclusively of epithelial origin. The aveolar sarcomas (2), recorded by Rehn; Marchand; Wendel; and Leuenberger, were in all probability highly anaplastic carcinomas of sarcomatoid appearance. It may be added that typical squamous cell carcinomas, with or without cornifications, were seldom observed.

X. PATHOLOGICAL RELATIONS

The ratio of benign to malignant aniline tumors is one to three, according to Büttner. Gay calculated for a series of 124 tumors from various German sources a ratio of 1:2 and found a similar ratio in his first American series of 23 cases. In his latest communication, dealing with 61 cases, he has changed the ratio to 1:1. He attributed this discrepancy to the earlier discovery of the tumors in the American workers, because of the routine practice of cystoscopy, and saw in the observation supportive evidence for his contention that there is a transition from benign to malignant lesions with the passage of time. The comparative figures of tumors of unknown cause are: Joseph (1931), 34.3 per cent papilloma and 65.7 per cent carcinoma; Voelcker and Boenninghaus, 76 per cent malignant tumors among 1,472 epithelial neoplasms of the bladder; American Urological Association Registry, 19.5 per cent benign lesions among 851 tumors.

The biological behavior of the aniline tumors varies considerably, depending to a certain extent on their histological structure. Benign villous papilloma may remain stationary or show only progressive local growth for many years, without producing symptoms except those of recurrent hemorrhages, which, however, may be very severe. It may become, on the other hand, rapidly malignant, especially following incomplete removal. Suddenness of appearance and, occasionally, astonishing rapidity of growth may be observed with benign as well as with malignant lesions.

It is asserted generally that bladder tumors, regardless of etiology, metastasize late if at all (Hueckel). Only 23 per cent of cryptogenetic bladder carcinomas in men and 32 per cent in women produced metastases, according to Posner. A similar percentage was cited by Cunningham. Metastases into the regionary lymph nodes were observed by Bilz in 26.3 per cent of his cases, and in remote organs and nodes in 21.1 per cent (cited by Wilinski). Simon (1932) stated that aniline tumors, while histologically identical with bladder tumors of unknown genesis, are biologically more benign than the

latter, as in 81 cases he did not observe *in vivo* or at autopsy any metastatic deposits. His optimism was not shared, however, by Mueller (1936), who pointed out that, according to the observations made in the Basel district, aniline tumors are extraordinarily malignant, and frequently and readily form distant metastases.

Metastases were present in the various organs (lymph nodes up to the supraclavicular fossae, vertebrae, skin, lungs, suprarenals, brain) of 11 of 17 fatalities which came to autopsy (Brezina; Simon) and for which detailed data were available in the literature. In 8 of these cases, remote organs were involved by secondary deposits. In none of the 5 American cases, in which autopsy was made, were metastases found (Gay). In 3 instances, however, there was primary carcinoma in other organs (skin, pancreas, kidney). The explanation of the apparently fundamentally different behavior of aniline tumors in different regions and different industrial plants is not evident. Experiences with other occupational cancers and with experimental tar and dibenzanthracene tumors suggest that such differences may be attributable to marked variations in the degree and length of exposure to the carcinogenic agent. It is a well known fact that the number of malignant tumors and the appearance of metastases depend to a certain extent on these factors, and a massive exposure to a carcinogenic agent may cause the development of neoplasms in usually less exposed organs.

Multiplicity is as frequent among bladder tumors having their origin in exposure to aromatic amines as among those of unknown genesis (for the latter Albarran gives the frequency of multiplicity as 25 per cent). The relation for aniline tumors is demonstrated in the following analysis of 98 instances reported in the literature.

	Papilloma	*Carcinoma*	*Total*
Single	21	57	78
Multiple	3	17	20

Washburn with 63 cases listed 24 as multiple and 39 as single.

Benign and malignant tumors may coexist in the same bladder, and multiple neoplasms of the same biological type (malignant or benign) may show marked differences in histologic structure (Wendel; Oppenheimer (1920 and 1926); Gay). This marked variation in histological structure of multiple neoplasms in a particular bladder was especially impressive in dogs treated with beta-naphthylamine (Hueper, Wiley and Wolfe). Among 50 or more lesions present at one time, practically all types of preneoplastic and neoplastic conditions were found. This factor, in addition to the histological evidence of multiple intraepithelial lesions, is sufficient proof that the multiplicity of aniline tumors is primary and not caused by secondary mucosal extensions from one tumor. Examination of the mucosa of the bladder in dogs with general papillomatosis frequently showed, near the base of well developed

tumors, small foci of irregular and atypical epithelium which were entirely unrelated to the neoplastic formations but which represented minute preneoplastic lesions.

XI. LOCALIZATION AND THE DEVELOPMENTAL MECHANISM

In spite of the fact that carcinogenic aromatic amines or their organic conversion products circulate in the blood, tumors are formed almost exclusively in the bladder, rarely in any other part of the urogenic tract (kidney, renal pelvis, ureter) (Rehn, 1906; Marchand; Sebening; Leuenberger; Oppenheimer, 1926; Mueller, 1936; Gay) and, as far as is known, never in the skin or in the digestive and respiratory organs, which are the sites of the most massive and direct primary contact and the ports of entrance of the aromatic amines to the organism. Theoretically, there are two ways by which the urinary epithelium of the bladder and the other parts of the urinary tract may come in contact with the carcinogenic agent. The carcinogen circulating in the blood may escape from the terminal capillaries into the mucosa and thus enter the epithelial cells—either directly or, after release into the contents of the bladder, by resorption. The second possibility is that the carcinogen, possibly produced from the original substances by metabolic action of the liver or of the kidneys, is excreted with the urine into the bladder and can then act on the mucosa for a prolonged period, until discharged.

The majority of investigators favor the last mentioned conception (Oppenheimer; Engel, 1937; Hueper, 1934; and others). It has been pointed out by them that the urine, containing the suspected carcinogenic substances, passes rather rapidly through the kidney, renal pelvis and ureters and that therefore these organs, as far as time of contact is concerned, are less exposed than the bladder, where the urine collects and remains for some time. In addition to the prolonged exposure of the bladder wall, there is the presence in the bladder of an increased amount of the carcinogenic agent, depending on the quality of urine contained in the lumen. It may be contended that this factor might be of importance by assuming that the concentration of the carcinogenic substances must reach a certain upper limit before a proliferative response is elicited; the same argument has been applied with reference to the concentration of aromatic amines in the blood to explain the absence of aniline tumors in other organs. Oppenheimer suggested that the carcinogenic substances are possibly precipitated from the urine on the wall of the bladder and act thereby directly on the mucosa. This conception may possess a certain merit, as the solubility of the urinary metabolites of the aromatic amines depends on the reaction of the urine, becoming progressively lower with increasing alkalinity of the urine. Precipitates thus formed would settle and collect on the floor of the bladder, i.e., the place in man where the majority of bladder tumors are situated. In this connection it may be mentioned that the reaction of the urine in dogs with experimental bladder tumors (Hueper,

Wiley and Wolfe) became definitely and, at times, strongly alkaline, though normally acid, many months before the tumors became manifest.

Kennaway considered the possibility that the potentially carcinogenic substance acquires cancer-producing qualities first under the chemical conditions which prevail in the urine. Since this change takes place rather slowly, the kidneys and ureters should tend to escape.

If these considerations are applied, additional support for the urogenous theory is obtained from the interrelations existing between the local distribution of the aniline tumors in the bladder and the anatomic conditions of the viscus, especially those of the floor. Aniline tumors in man are found most frequently in the trigonal and paratrigonal area and the lower posterior wall, i.e., in the dependent parts of the organ. Hueper (1934) found 60 of 81 tumors and Gay 11 of 17 tumors located in the region of the floor. A more detailed analysis of the distribution shows that there is crowding of tumors around the ureteral and urethral orifices, where a certain mechanical trauma from the urinary flow is present, and in the areas lateral to the plicae uretericae and in the fossa retroureterica, which represent the most dependent parts of the floor, as the area of the trigon is elevated slightly.

Local Distribution of Tumors in the Bladder

	Papilloma	*Carcinoma*	*Total*
Trigonal region	13	47	60
Elsewhere	2	19	21
Mixed (multiple tumors)		8	8

Bladder tumors of chemical etiology thus follow in their location and distribution in this viscus the cryptogenetic vesical neoplasms (Watson; Hueckel).

The marked significance of static conditions for the localization of the aniline tumors in the bladder has been further emphasized recently by observations made in dogs with experimental tumors (Hueper, Wiley and Wolfe). These investigators found that the great majority of the pretumorous and tumerous formations were located in the region of the dome and of the adjacent and mainly anterior parts of the bladder, where also the largest tumors were noted. On account of the different static conditions present in the dog, these areas represent the most dependent parts of this viscus when the dog is in a lying or a standing position. It may be added that a similar location of verrucous hyperplastic or papillomatous formations was observed in the bladder of mice after estrogen injections (Lascassagne), of rabbits after beta-naphthylamine injections into the subcutaneous tissue (Hueper, Briggs and Wolfe), and after instillations of watery and oily solutions of aniline and ortho-amino-azo-toluene into the bladder of rabbits (Yamazaki and Sato), that is, in animals where identical static conditions prevail as those present in the dog.

The normal differences in the density of vascularization between the floor

and the dome of the bladder are, therefore, not the controlling factors in this respect as claimed by Ferguson (1934 and 1937).

The importance of local urinary conditions in the localizations of aniline tumors is demonstrated further by observations of Sebening, Mueller (1936) and Gay. These investigators reported the occurrence of tumors in renal pelves in association with anatomic anomalies of the corresponding ureters which interfered with the free flow of urine through these conduits. A status of prolonged urinary retention and mucosal contact within the affected area thus was produced similar to that existing normally in the bladder. These factors may be considered on the bases of the urogenous theory as predisposing to the development of tumors in the region of the urinary tract situated above the obstruction.

The urogenous theory also receives support from the experimental histological observations recorded in regard to the sequence of cellular changes in the different layers of the bladder in dogs. The fact that the first cellular reactions developed in the epithelium strongly suggests action through urinary contact.

The hematogenous theory, sponsored by Ferguson and Gay, assumes that the carcinogenic agents circulating in the blood have a special affinity for the bladder tissue, causing there specific primary injury to the terminal capillaries of the submucosa of the bladder and other parts of the urinary tract. The validity of this hypothesis is supported, according to its authors, by the following evidence: 1. The majority of the aniline tumors occur in the lower half of the bladder, i.e., in the best vascularized part of the viscus, but do not involve most often its most dependent part, the trigonal area. 2. Aniline tumors develop not only in the bladder but also in the kidneys, renal pelves and ureters, indicating thereby a systemic and not merely a local organic affinity. 3. Histological examination of early lesions of the human bladder demonstrates that the vascular changes precede the epithelial reactions, which originate in the basal layer. 4. The mucosa in the vicinity of bladder tumors of occupational and nonoccupational origin does not show, on microscopic study, any sign of irritation, such as hyperplasia, which can be expected if action is through urinary contact. 5. Attempts to demonstrate a carcinogenic substance in the urine of persons with occupational and nonoccupational tumors have failed. 6. The urinary excretory metabolites of aromatic amines have been proved to be carcinogenically inert. 7. The assumption that there is an exclusive chemical tissue specificity in the causation of bladder tumors is not unique, as a similar hematogenous mechanism is claimed to be present in the causation of arsenical cancers, the occurrence of which is restricted to the skin.

The hematogenous theory is an interesting conception which deserves further investigation, especially with experimental methods. Ferguson proposed, to this end, transplanting the ureters of an animal into the rectum

and to thus exclude the bladder mucosa from any contact with urine, leaving only the possibility of hematogenous action. A positive outcome of such an experiment, i.e., the formation of bladder tumors, would greatly support the hematogenous theory. But a negative result would not disprove it entirely, as one might argue that the marked impairment of the circulation of the blood in the functionally inactive bladder might have influenced its reactivity. Hueper suggested therefore that one or both ureters of the female dog be explanted to the uterine horns or to a rectal pouch serving as an artificial bladder and that a sigmoidostomy be done to take care of the fecal eliminations. The appearance of tumors in the uterus or in the rectal "bladder" would indicate that the urine contained carcinogenic agents.

The factual evidence available at present lends little support to the hematogenous conception. Many of the serious objections which may be raised against its validity are contained in the discussion of the data favoring the urogenic origin of aniline tumors. They do not need to be repeated. There are, however, a few points which may be worth considering in this connection.

The hematogenous theory actually assumes the presence of a two-fold affinity: a primary, purely chemical, one of the terminal capillaries in the submucosa only, exempting the elements of the second vascular network located in the muscularis; and a secondary carcinogenic epithelial affinity, leaving the primarily involved mesenchymal elements unaffected, as so far practically none of the aniline tumors has been of a sarcomatous type. Such a selective behavior of a chemical carcinogen, which cannot be accounted for by any known special chemical secretory or excretory qualities of the bladder mucosa, must appear extraordinary in view of the well established faculty of the various synthetic carcinogenic chemicals to elicit carcinomatous as well as sarcomatous responses, depending mainly on the type of tissue with which immediate contact occurs. A comparison with arsenical carcinoma scarcely is justified, for not only does the skin possess a known chemical affinity for arsenic and, therefore, stores it and excretes it with the sulfur-containing compounds contained in keratin and hair, but arsenic causes a fundamental disturbance in the distribution and production of melanin. In a discussion of the interrelations apparently existing between the agent and the soil in carcinogenesis, Woglom also supported the conception of an organ specificity of the bladder to aromatic amines. He contended that aniline produces tumors only in the bladder, but not in other parts of the urogenous tract, that is, the kidney and the ureter. Inasmuch as this argument is contrary to the facts recorded above, his assertion can be discounted justly.

Reference must be made to some observations made by Schär, who concluded, from his experiments on the resorptive and excretory properties of the vesical mucosa, that this membrane possesses a secretory as well as resorptive function. Naphthylamine present in the urine and coming in contact with the epithelial cells of the vesical mucosa may be resorbed therefore into these

cells and may become precipitated around the submucosal vessels. Beta-naphthylamine contained in the blood, on the other hand, may be released from the mucosal capillaries into the epithelial lining and may be excreted by them into the urine. Schär contends, that a cancerization of the epithelium occurs only, if minimal quantities of the suspected aromatic amines act upon the mucosa, while an exposure to large amounts of these chemicals does not exert a carcinogenic action. While the excretory function of the vesical epithelium alleged by Schär must remain problematical, the experiments of Mann and Magoun with phenolsulphophthalein and the extensive investigations of Hishikawa with numerous basic and acid aniline dyes have established definitely the fact that the normal bladder mucosa in mammalians is capable of resorbing appreciable quantities of these substances. This permeability, however, is markedly increased and is extended to dyes which normally do not penetrate the bladder lining if inflammatory changes in the vesical mucosa exist. The author, several years ago, conducted some preliminary investigative work on lines similar to those followed by Schär which elucidates some of the observations made by this investigator.

The purpose of the experiments was an attempt to demonstrate beta-naphthylamine in the tissues with the help of color reactions. Nitro-aniline, diazotized by the addition of a small amount of sodium nitrite, was used as a reagent, since a watery solution of this compound (10 per cent nitro-aniline plus a few drops of 5 per cent solution of sodium nitrite) gives, when coming in contact with even very small amounts of beta-naphthylamine, an intensely cerise red precipitate.

Mice, which had been given subcutaneous injections of 0.01 gm. of beta-naphthylamine, were opened after from one to two hours while still living. A freshly prepared mixture of the reagent described was dropped on the bladder, liver, kidney and finally the lungs. The organs were studied with a Zeiss epicondenser under direct reflected light. Accumulations of reddish granules were seen in the superficial cells of the liver (hepatic cells and Kupffer cells) and of the kidney (tubular epithelium and lumens). When this reagent was injected directly into the bladder filled with brown urine, a heavy red precipitate was formed. Following intracardial injections of the reagent, orange-red granular deposits were observed in the wall of the bladder, especially in the lumens and perivascular tissue of blood vessels. The epithelium of the bladder appeared to be without colored matter, except some cells with fine, dustlike, red-brown granules located in their cytoplasm. These observations were substantiated on unstained frozen sections prepared from unfixed tissue with the cooled knife method (Hueper, 1934).

A second series of mice, which were given subcutaneous injections of 0.002 gm. of beta-naphthylamine hydrochloride three times at four-day intervals, were killed in pairs—three, five and ten days after the last injection. None of the organs tested showed any color reaction, grossly or microscopically. The

retroperitoneal and perivesical fat tissue gave, three days after the last injection, an orange-red color when the reagent was dropped on it. A faintly positive reaction was obtained up to five days after the injection.

The observations reported indicate that intravascular and perivascular precipitations of beta-naphthylamine are, apparently, the result of an acute toxic effect when the organism is flooded with this substance. On the other hand, it was quite evident that the urine not only contained a higher amount of the aromatic amine but continued to show it in demonstrable traces for a longer period than any of the parenchymatous organs tested. It is reasonable to assume, therefore, that under ordinary metatoxic conditions of exposure, the main and, probably, the only contact of the epithelium of the bladder with the carcinogenic agent takes place on the mucosal surface.

It appears premature to attach definite significance to the failure to demonstrate carcinogenic substances in the urine of persons with bladder tumors. The technical methods used for chemical extraction and experimental testing doubtlessly were inadequate for this task, as Steele, Koch and Steiner showed recently that butyl alcohol extracts prepared from the urine of normal and cancer bearing individuals produced malignant tumors when injected into mice.

The present state of knowledge also does not permit any final statement in regard to the potential carcinogenic qualities of the urinary metabolites of aromatic amines, as only some of them are known actually and definitely identified, while none of them yet has been tested reliably for carcinogenic properties. Some time ago the author experimented with an impure 2-amino-1-naphthol, one of the known urinary excretory products from beta-naphthylamine. Concentrated solutions of this substance in olive oil and rabbit serum, respectively, were injected intraperitoneally into white mice of common stock in individual doses of 0.1 cc. twice weekly for a period of approximately six months. There were 25 animals in each series. Histological examinations were made of 36 mice. The following neoplastic formations were found in this group: retrothelial sarcoma in 3, myeloid leukemia in 1, pulmonary adenoma in 5, splenic hemangioma in 1 and sebaceous gland adenoma in 1. While the evidence presented is suggestive that the tumorous conditions are, at least in part, attributable to the treatment given, it is far from conclusive.

The predominant location of bladder tumors in the region of the bladder floor has been ascribed also to embryonic developmental disturbances, which frequently involve this area and cause the production of tissue malformations and misplacements. These cell complexes represent, according to the Cohnheim-Ribbert theory, a tissue predisposed to the formation of tumors. The experimental observations which were made in dogs (Hueper) concerning the numerous minute foci of atypical epithelial proliferations and the local shift of the canine tumors toward the dome demonstrate definitely that the conception of Cohnheim as to the genesis of tumors has no place in the explanation of the causative mechanism of aniline tumors.

The trigonal prevalence and causation of aniline tumors have been related also to the chronic inflammatory processes which frequently occur in this part of the bladder, on the assumption that exposure to aromatic amines results in chronic cystitis. The further course of events is then readily explainable by the application of Virchow's theory of chronic irritation. The histological observations which the author made on dogs, and those reported by Perlmann and Staehler (1932 and 1933) on rabbits, indicate that Virchow's theory cannot be applied to aniline tumors. Whenever chronic inflammatory changes were present in association with preneoplastic or neoplastic lesions, they were secondary and coincidental but not causative. In consideration of the absence of tumor formation in the great majority of cases of chronic chemical occupational dermatoses and pulmonary conditions, chronic nonspecific irritation appears to be highly overrated as a carcinogenic factor (Oppenheim). Aniline tumors are not phenomena of secondary epithelial growth on the basis of a chronically inflamed and impaired supporting tissue. Neither symptomatic nor morphologic evidence supports such a conception.

XII. TREATMENT

It may suffice to state here that the indications for therapy and the methods used in the management of aniline tumors are identical with those for bladder tumors in general. Surgical excision, electrocoagulation, irradiation with roentgen-rays and treatment with radium emanation have been employed. According to the experiences of Simon (1932), Mueller (1936), Ferguson (1937) and Washburn, these tumors respond to irradiation. Mueller stated, however, that the metastatic tumors react more readily to this therapy than the primary growths in the bladder. In view of the frequent multiplicity of aniline tumors, therapeutic measures which affect the entire viscus, without causing functional impairment, deserve special consideration.

A new and still experimental method of therapeutic attack has been proposed by Henschen. Following the thoughts of Bauer in regard to the therapeutic effect of the application of minute amounts of 3.4-benzpyrene to skin cancers, Henschen has administered, during the last two years to his patients, with bladder tumors, small amounts of naphthylamine by mouth. He believes that the contact of the naphthylamine with the carcinogenic agent in the wall of the bladder, partially or totally, inactivates the carcinogen. The preliminary results obtained with this method are, according to its author, promising.

XIII. PROGNOSIS

The final outcome of any neoplastic disease depends on various factors, such as the degree of malignancy (local and metastatic activity of growth), the extent and location of the tumor, the age and general condition of the patient, and the type and quality of the therapeutic procedures. An accurate prognostication of bladder tumors, especially those of chemical etiology, is

complicated, moreover, by the fact that recurrences or new growths may appear many years (15 to 20) after the removal and apparent cure of the first neoplasm. The high incidence of primary recurrences in the bladder of these workers may be gaged from an observation by Washburn, who reported that within five years eleven out of a total of twenty-two cases with papillomas developed new growths in the bladder. The curative results reported by various authors differ, therefore, considerably. It must be pointed out in this connection that even a benign papilloma may prove fatal in the long run because of its tendency to recur and, in some instances, to bleed profusely (Engel, 1937).

In the older statistics, the mortality among diseased workers is shown to have been high, especially regarding cancers caused by aniline, which Leuenberger considered as having an unfavorable prognosis. The curative prospects are low also in cases with multiple, sessile or highly anaplastic tumors (Washburn). Oppenheimer recorded the mortality as 73.5 per cent; Schwerin, as 66 per cent. Of Nassauer's 32 patients, 27 are dead; of Büttner's 10 patients, 5 have died; of Leuenberger's 18 patients, 11 have succumbed. But the figures of the two last-mentioned authors are not final, as some of the patients have been observed only a short time, and the ultimate fate of others is unknown. Mueller (1936) stated that 7 of his 36 cancerous patients were still living. The average duration of disease in his fatal cases was two years and a half. Death often was due to an ascending renal infection and urinary sepsis. In all of his cases the tumors proved to be very malignant and ran a rapid course. Mueller (1931) emphasized the fact that the clinical extent of the tumor in the bladder offers no information about the extravesical distribution of the tumor.

A much more favorable prognosis has been given recently to aniline tumors by Simon (1932). Bladder tumors with their genesis in exposure to aromatic amines run, according to him, a slower course and respond better to the various therapeutic procedures than bladder tumors of unknown origin. He reported three year arrests in 54 per cent and five year arrests in 48 per cent of his 81 cases of aniline carcinoma, whereas there were five year arrests in only 10.5 per cent of his cases of bladder tumors of unknown origin. Similarly favorable results were reported by Washburn. Among 86 patients there were 9 deaths, 7 of them directly or indirectly attributable to the neoplasms. Fifty-two (62 per cent) of the patients were tumor-free for varying lengths of time. Washburn ascribed these good results in part to the fact that the tumors were discovered in a rather early stage through the routine practice of cystoscopy. It appears doubtful, however, whether these good results will be maintained permanently, as the workers of this group have returned to the hazardous operation and their bladders are exposed again to the action of the carcinogenic agent. This may activate any latent preneoplastic mucosal lesion preexisting from the former exposure. Such a course must be expected, ac-

cording to experiences with occupational and experimental tar and pitch tumors. The possibility exists, therefore, that recurrences may be more frequent in this series than they would be if the exposure had been terminated completely after the discovery of the first tumor. All available data indicate that prognosis of aniline tumors does not differ essentially in any way from those of the cryptogenetic type, when the same standards of comparison are applied (Berenblum; Hueckel).

XIV. SUSCEPTIBILITY

In many clinical reports reference is made to an apparent difference in individual susceptibility among workmen in the presence of an identical type and duration of exposure. Some of the variations in personal reactivity are certainly only apparent, i.e., they are referable to differences in cleanliness, working habits and general intelligence. These factors may have an important influence on the amount of exposure received. But, doubtlessly some of the discrepancies are of a personal or constitutional nature. Factors which may be of causative importance are, according to Berenblum, either true differences in the reactivity of the bladder mucosa, or individual variation in the absorption of the carcinogenic substances or in their alterations occurring in the body, or in their rate of excretion.

Such variations in neoplastic responsiveness were also evident among dogs used in the experiments of Hueper, Wiley and Wolfe. While the first dogs presented tumors after twenty months of treatment, two were still cystoscopically free from pathological manifestations after thirty months of exposure. As the microscopic examination of the bladder of one of these dogs showed the presence of a minute carcinomatous lesion, it stands to reason that any degree of personal resistance against chemical tumor formation may be overcome ultimately if the exposure to the aromatic amine is sufficiently long and intense. The high frequency of bladder tumors among certain groups of dye workers confirms this conception. From an analysis of a larger series of case histories of aniline tumors, it is the author's impression that hereditary factors, especially those indicating a special organ susceptibility do not play any significant role in the neoplastic responses observed. This is in spite of the fact that Anderson reported a positive cancer history in the family of four out of twenty-five cases of aniline tumors (17 per cent). If any congenital predisposition exists, it must have the character of a general special reactivity to the carcinogenic chemicals, which, in the main, seems to be a matter of gradual development and artificial acquisition. The site of the tumor, the bladder, is merely the result of metabolic and excretory conditions which are peculiar to the type of chemical and which determine the tissue of most pronounced contact.

From observations made in man so far, it may appear as though only the male sex is susceptible to aniline tumors. This has its plausible explanation

in the fact that, normally, only men are employed in these operations. The experimental production of these tumors in female dogs indicates that no difference occurs on a sex basis.

XV. OCCUPATION

The majority of the observed aniline tumors occurred in workers engaged in the production of aromatic amines and in the manufacture of aniline dyes from aromatic amines. While all operators, helpers, laborers, foremen, and repairmen employed in these operations come into contact to some extent with chemical agents exerting their carcinogenic action mainly in the bladder, there exist among them appreciable differences in the degree of exposure, depending upon the type of work in which they are engaged.

1. During the early days of synthetic dye production, when precautions were not taken to prevent the escape of aniline fumes from open containers, workers employed in the bomb and melting rooms, in rooms where the crude aniline was distilled and where nitrobenzol was reduced to aniline (reduction rooms) labored in an atmosphere heavily charged with aniline fumes. These individuals were the most frequent victims of aniline tumors. Another place overlooked for a long time, in which aniline fumes were generated (Nassauer), was the room in which the final distillation of pure benzidine took place. Here a small amount of benzidine was converted into aniline in the boilers because of the high temperature present and the reduction atmosphere employed. Aniline fumes were formed also during the production of dyes from pure powdered benzidine when this chemical was dissolved in hydrochloric acid. The hazard in this case, however, was of minor significance, as the aniline produced was removed subsequently during the diazotization and the formation of the finished product (dianisidin, congo red, benzopurpurin), and thus ceased to be an immediate source of danger.

The main hazards connected with the production of alpha-naphthylamine and beta-naphthylamine, as well as benzidine, is the inhalation of dust, when these chemicals are ground, bagged and barrelled (Mueller), and of fumes generated during autoclaving, drying and baking processes connected with the manufacture of alkylated and arylated bases and sulfonic acids (Engel).

Carcinogenic substances are formed also during the production of aniline dyes, benzoic acid compounds and artificial indigo from toluidine ($C_6H_4(CH_3)(NH_2)$), a substance chemically closely related to aniline. The workers engaged in the reduction of nitronaphthalene into naphthylamine used for the production of Martius yellow (for dyeing wool) and Magdala red (for dyeing silk), are exposed more to contact with carcinogenic chemicals of the aromatic amine type than the other dye workers. An additional and marked exposure to these agents occurs during the removal of the tarry sludge accumulated in the stills and pipes by the workmen, unless special

precautions are taken as well as proper supervision exercised by a foreman familiar with the hazards involved.

In numerous plants of modern construction and where there is conscientious management, a great many of the various hazards listed either have been completely eliminated or reduced greatly by the introduction of a closed system of production, installation of an efficient and properly placed exhaust ventilation and other sanitary measures. Any escape of fumes and dust in such plants, owing to leaks in pipe connections and similar defects, is mainly accidental. On the other hand, the occurrence of numerous aniline tumors among workers of some plants in recent years provides weighty evidence that in these establishments a great hazard still exists and that improvement is needed urgently.

2. The second group of men exposed to carcinogenic aromatic amines consists of workers who enter at irregular intervals the rooms in which these chemicals are manufactured or handled. They are special workers, such as plumbers, bricklayers, pipefitters, millwrights, carpenters, and mechanics. While their contact with the carcinogenic agents is not constant, it is usually rather intimate and is associated with the carrying on of repair work. This task involves the handling of parts of machinery (stills, boilers, autoclaves, pipes), covered with aromatic amines and tarry sludge, as well as lumber and bricks saturated with these chemicals. There is approximately a total of twenty of these workers on record with aniline tumors (Leuenberger; Nassauer; Oppenheimer; Hueper).

3. A third, but relatively small group of exposed persons, is represented by chemists and laboratory assistants who analyze and test the various products used in the manufacture of synthetic dyes. The occurrence of bladder tumors of aromatic amine genesis among members of this occupational group was reported by Leuenberger; Nassauer; Oppenheimer, and Wolfe.

4. A fourth group of individuals who may develop aniline tumors of the urogenous organs, in spite of the fact that they have no direct occupational contact with the carcinogenic chemicals, but who work or live in the immediate vicinity of their production and thus may be exposed to the inhalation of fumes, dust and vapors containing aromatic amines in low concentration, is composed of managers, clerks, drivers, and yard workers (Oppenheimer; Nassauer; Hueper) employed in the dye works.

5. A fifth group of workers among whom the occurrence of aniline tumors has been observed (Schueller; Rosenbaum and Gottlieb; Gay; Leuenberger; Joseph; Fierz-David) consists of persons handling the finished products. These may be dye grinders, mixers, attendants of dye storage houses and dyers. The dyers, pressing hot aniline dyes upon fabrics, are especially endangered, according to Leuenberger.

The carcinogenic potency of aniline dyes has been disputed by numerous investigators until recent times. Gehrmann as late as 1934 stated that the

experience of manufacturers in this country, England, Germany and Switzerland would prove definitely that the handling and use of the finished products are responsible in no way for the development of occupational bladder tumors. This statement of Gehrmann, however, lacks convincing proof in the absence of any published data on systematic, extensive and trustworthy investigations of this aspect. There exist only two references in the literature concerning the incidence of bladder tumors among dyers or related workers. The absence of bladder tumors, among approximately 300 dyers in various establishments surveyed, was noted by Schueller. Similarly, no instance of this disease could be found by Judin (U.S.S.R.) among 9,000 textile workers examined. Both observations, however, are of questionable significance, as no adequate consideration is given to certain essential factors, such as, duration and type of exposure to dyes or the chemical character of the dyes used.

In this respect also it is not proper to rely upon the cutaneous reactions which may be elicited in the skin of man and animals by the external application or cutaneous introduction of certain dyes. Experiments of this type, conducted by Fischer-Wasels; Stoeber; Jores; Sachs; Schmincke and many others, with ortho-amino-azo-benzol (sudan III) and chemically related dyes (scarlet red, brilliant red, yellow light, acid yellow) have shown that transitory, epithelioma-like proliferations can be elicited in animals by the subcutaneous injection of these dyes, usually in the form of oily solutions. While such epitheliomatoid, verrucous lesions can be produced rather readily in the skin of animals, such reactions are rare in human skin, when these dyes are applied superficially (Koelsch).

The recent investigations of Japanese, American, and German investigators have clearly shown, on the other hand, that amino-azo-benzol, amino-azo-toluol, p-dimethyl-aminobenzene, 4'hydroxy-2:3-azo-toluene, benzyl-ethyl-aniline are not only the cause of malignant tumors in the liver and stomach of experimental animals, receiving these dyes in their diet or injected subcutaneously with them, but are also the chemical stimulus for the development of bladder tumors when administered orally or instilled directly into the bladder (Yoshida; Kinosita; Yamazaki and Nagao; Shear; Butenandt; and others).

6. The last group of persons, to be mentioned in this connection, is composed of individuals who neither live nor work in the dye factory and have no occupational contact with the carcinogenic aromatic chemicals. The homes of these people are located in the immediate vicinity of the plants and thus they live within the environmental fume and dust zone of these establishments. This type of purely environmental, non-occupational aniline tumor of the bladder is represented by eight cases in the series of amino-tumors reported by Nassauer. While the actual justification for the existence of this group has been disputed and doubted repeatedly (Posner; Oppenheimer; Buettner), and whereas no convincing proof, in support of this contention, has

been offered by Nassauer, certain precautionary measures taken by the German plants in regard to a more effective removal of fumes from the wastes released into the atmosphere indicate that Nassauer's warning was perhaps not entirely without cause. The recognized occurrence of aniline tumors in yard workers employed within the plant district furnishes circumstantial evidence supporting the possibility of the existence of purely environmental aniline tumors among the civil population living in the fume zone of dye plants.

It is apparent that the actuality of such neoplasms depends to a great extent upon the precautionary measures taken in the various plants to prevent the production of carcinogenic dust and the release of fumes containing the carcinogenic agents into the air. Wherever the most fundamental requirements of cleanliness within the plants are lacking, considerable quantities of carcinogenic aromatic amines may enter the air in chemical factories, from which source persons, living beyond the limits of the plant proper, may be endangered. Contamination of the surrounding air in the vicinity of dye factories is brought about by the use of a system of exhaust ventilation without the use of filters or neutralization equipment which delivers the contaminated fumes directly into the air above the buildings. The carcinogenic agent contained in the exhaust material is permitted to spread in the low strata of the air. The installation of high stacks for the removal of fumes and exhausts, on the other hand, is apt to overcome, at least partially, such a danger. Appreciable quantities of aromatic amines may enter the air also when these substances are spilled from the bags while being loaded on outside platforms. The same hazard may be produced when these chemicals are swept, during the cleaning of workrooms, into open drainage ditches, through which they may be carried not only into more remote parts of the factory district but from which they may be carried away by high winds in dry weather and thus spread over a wide area beyond the confines of the factory.

XVI. PROTECTIVE AND PREVENTIVE MEASURES

After the recognition of the existence of etiological interrelations between the exposure to aromatic amino-compounds and the development of neoplasms of the urogenous tract, numerous preventive and protective measures have been proposed. Some have been introduced in many factories manufacturing and handling carcinogenic chemicals. This development started in Germany in 1904, soon after the discovery of the first aniline tumors. It has resulted ultimately in the erection of new plants, in the construction of which were embodied the experiences collected over a number of years. It seems to be doubtful, however, whether many of the observations made and precautions taken in Germany and Switzerland were utilized properly in the countries with a more recent chemical industrial development. The high incidence of bladder tumors among the dye workers of these countries indicates that

the published reports concerning the German and Swiss experiences, and the technical and medical measures taken, remained either unknown or were disregarded in the initial construction of the dye works in the countries with post-World War chemical industrial development.

A. *Factory Measures*

a. Technical methods were devised to eliminate or restrict to a large extent the free escape of fumes as well as the production of dust of aromatic amines which were connected unavoidably with the use of open containers in the manufacture of synthetic dyes. This task was accomplished successfully by the introduction of the closed system of production, in which compressed air is used to convey the chemicals from one container into the next through fume-tight pipe lines. Modifications were made also in the technique employed for the routine analysis and identification of the chemical qualities of the carcinogenic products, thus obviating any direct contact of the chemist with the substances examined.

b. These measures were supplemented by the installation of an elaborate and adequate exhaust ventilation system, wherever necessary, in places where the danger of leaks in pipe lines existed, where the escape of fumes and the production of dust could not be excluded entirely, and where apparatus had to be cleaned and repaired at regular intervals.

c. High stacks (200 feet) were erected and equipped with neutralizing apparatus through which exhaust fumes were released into the higher strata of the air. From here they could not be blown easily into nearby buildings. By reducing the amount of carcinogenic substances which were allowed heretofore to contaminate the air of the plant district, the possible danger of cancer production in persons working or living in the fume zone of the factories, was diminished markedly or removed entirely.

d. Special regulations were issued controlling the procedure of repair work on apparatus used for the production of carcinogenic aromatic amines. This work is done in some plants only in the presence of and under the supervision of a specially trained member of the safety department, who is independent of the department manager. The workers engaged in such tasks are obliged to wear special protective clothing (rubberized) and masks. Nassauer advised the removal of all workers not used directly for the repair work from the room, especially when the repair involves pipe lines and boilers. Repairs on boilers and stills should be done only after these containers are cooled.

e. Attention may be called also to the fact that a floor covering which absorbs aromatic amines, such as asphalt, is unsuitable for use in rooms in which these substances are produced or handled. The same consideration may be applied to ordinary porous brick and wood in the construction of buildings to be used for this purpose, as these building materials take up considerable quantities of aromatic amines from the fumes and dust produced. In the con-

struction of such plants the use of glazed brick is recommended since it can be cleaned easily with water. The installation of machinery, apparatus and pipe lines should be such that little opportunity is offered for the deposition of dust by the elimination of nooks and crevices. Such an arrangement would facilitate greatly the regular cleaning of work rooms.

f. Methods were developed through which the production of carcinogenic substances in various operations or their retention as impurities in the finished products were either partially or entirely obviated. Many of the dyes manufactured in late years have become chemically purer than formerly.

g. The following measures were suggested by Nassauer for the protection of the workers from any direct contact with the carcinogenic chemicals:

Special, closely fitting work clothes to be kept in lockers, separate from street clothes. The locker rooms should be remote from the work rooms to prevent any saturation of the street clothes by the fumes produced (Sieben). The work clothes should be laundered frequently, at least weekly.

Wooden shoes, rubber gloves and face masks should be worn. The latter device appears to be essential, especially for the protection of those workers who fill bags or barrels with ground aromatic amines.

Shower baths should be provided and baths should be taken after each working shift. Bathing should be made obligatory and should be carried out under supervision of the foreman.

Toilets should be readily available and near the work rooms to avoid undue prolonged retention of urine in the bladder. Frequent urination should be encouraged by providing free beverages, especially during the hot season.

Separate lunch rooms should be provided for the workers. These individuals should be obliged to wash their faces and hands before meals and no food should be permitted to be brought into the workrooms.

It should be made the special duty of the foremen and supervisors of such operations to enforce these regulations.

B. *Medical Measures*

a. Men to be employed in the manufacture of synthetic dyes should be strong and healthy. Their ages should range from twenty to forty-five years.

b. The previous occupational history of every applicant should be examined closely for any preceding exposure to aromatic amines and for any manifestations indicating the existence of a hypersensitivity to aromatic chemicals.

c. Persons with a definite family history of a high cancer incidence should be excluded from the employment in these operations. Such individuals possess perhaps a higher susceptibility to the carcinogenic action of aromatic amines than individuals without such a history. It must be admitted that the basis for this recommendation is mainly speculative, as no reliable evidence based upon human observations exists. Observations made upon mice suggest,

however, that an inherited predisposition of various organs to cancer is not a reliable index as to the reactivity of these organs to a stimulus provided by a known carcinogenic chemical (Andervont).

d. A thorough physical examination should be made, to determine if the applicant is in perfect health. The examinations should include an analysis of the urine and of the blood as well as a test for syphilis. Whenever possible, a cystoscopic examination should be made to determine the absence of any pathology in the urethra, bladder and prostate. Special significance should be attached to the presence of any hepatic, cardiovascular and urogenous disorders. Alcoholics should not be accepted for this type of work. Men of low mentality and unclean habits are considered unsuited.

e. The urine of all workers employed in these operations should be analyzed at regular intervals of not less than 3 months. Special attention should be paid to the presence of blood in the urine. Such a finding should be an imperative indication for an immediate cystoscopic examination, unless the hematuria was associated with an acute attack of anilism. The Kuchenbecker test for aromatic amines may be of value upon special occasions.

f. Workers should be thoroughly instructed regarding the dangers involved. They should be cautioned to seek medical aid immediately at the first appearance of a suspicious symptom, especially urinary symptoms (Scheele).

g. Periodical cystoscopic examinations have been advised as a routine measure by various investigators (Ullmann; Oppenheimer; Gehrmann; Baader; Hueper). Cystoscopic examinations, on all workers who are exposed more or less to aromatic amines in intervals of 6 to 12 months, represent the only reliable method for the early discovery of aniline tumors. They aid considerably in effective therapeutic control of this neoplastic condition. Periodical cystoscopic examinations should be made compulsory for all workers employed in operations involving contact with aromatic amines and synthetic dyes of known or suspected carcinogenic properties. In view of the known long latency period of aniline tumors, it appears essential that these cystoscopic examinations shall be continued for many years after cessation of exposure to these agents (due to retirement or change of occupation) (Heusch).

h. The attitude of the administrative and medical management of dye plants regarding the maximum time workers should be permitted to stay in the aromatic amine operations has remained confused and unsettled. All German medical authorities, who expressed an opinion upon this subject, recommended that workers should be removed from the hazardous operations after a limited period of employment ranging from 2 months to 3 years (Nassauer; Oppenheimer; Posner). These individuals should be replaced by workers not previously exposed. It is obvious that such a policy when

carried out in practice would not only be disadvantageous to the maintenance of efficient working conditions and to a continuous employment of experienced workers, but it does not appear to be warranted for plants properly constructed and conducted in regard to the observance of adequate preventive and precautionary technical and medical measures. The replacement of workers after more than one year's employment would result, moreover, in the production of a large number of persons requiring a prolonged medical and social supervision, as any period of exposure surpassing one year can be considered as sufficient to cause in some persons a cancerigenic response. The adoption of such a policy would not only be expensive and cumbersome to apply but, in all probability, would not result in a decrease of the incidence of aniline tumors. The data published do not indicate whether or not such policy was ever observed for any period in any of the German plants.

Some American factories adopted a different procedure which they patterned, according to the statement of Gehrmann, after the system operative for some time in the large German chemical establishments: A worker once placed in an aromatic amine area is never transferred elsewhere. If he develops aniline tumors and recovers after treatment, he is returned to his former work, as it is held that his chances to develop recurrences or new tumors are not lessened by his removal from the hazardous work. Without doubt such a policy accomplishes one aim, the number of exposed workers is restricted. By keeping this number at a minimum the expenses for compensation are maintained at a low figure. It is, on the other hand, certain that the reasoning advanced to justify this procedure is incorrect. Evidence obtained from experimental carcinogenesis, as well as observations made with various occupational cancers, show conclusively that a continuation of the exposure to carcinogenic agents lessens seriously the prospects of a permanent cure from an occupational neoplasm and stimulates the occurrence of new primary tumors as to time (earlier appearance) and incidence (multiplicity). It may be mentioned in this connection that such a policy was not in force at any time in any German plant, according to reliable information, obtained in recent years. The statement made by Gehrmann to this effect is obviously the result of a misunderstanding. German dye workers developing neoplastic or preneoplastic bladder lesions are removed immediately from the hazardous operation and at no time are returned to it.

Such a policy appears to be under the present circumstances the one most to be recommended, provided that, at the same time, all efforts are made to restrict contact of dye workers with the carcinogenic chemicals. This may be accomplished by using the most advanced technical methods of production and by the observance and enforcement of sanitary and medical precautionary measures. The elimination of this type of occupational tumor is not so much a matter of medical concern as it is a task of proper chemical engineering, and could be accomplished provided the necessary and needed stimuli were present.

XVII. MEDICO-LEGAL ASPECTS

The first request for governmental regulations protecting workers employed in the dye stuff industry was made by Leichtenstern in 1898, three years after the discovery of the aniline tumors by Rehn. It was not, however, until 1925 that the German government passed a law (§ 1552 R.V.O. and § 8 I.V.O.) by which the tumors of the bladder, resulting from an occupational exposure to aromatic amines, were included among the occupational diseases requiring compensation. At the same time notification of their occurrence to the governmental health authorities was made obligatory. Switzerland recognized aniline tumors as an occupational disease in 1920; England followed in 1932, and similar laws were put in force in recent years in Russia, Italy, Czechoslovakia, Belgium, France, Canada, Australia and several of the states of the United States of America (Minnesota, New Jersey, Ohio, California, Connecticut, North Dakota, Illinois, Wisconsin, New York, Massachusetts, Missouri, etc. (International Labour Conference)).

In an appreciable number of states (of the United States) compensation laws do not exist, while in others, until recently, the regulations are worded in such a way that they provide insufficient protection to the worker, since they do not take into proper account the long latency period of these tumors (New Jersey, Minnesota, Porto Rico, etc.) (*Industrial Medicine*, 1933).

It is quite obvious that a law restricting eligibility to compensation to a maximum period of five or six months after the cessation of occupational exposure is wholly inadequate to cover the existing situation. The same objection must be raised against the laws which limit compensability to certain chemicals and their derivatives.

The preceding presentation has made it clear that a variety of chemicals of aromatic character may cause the development of benign and malignant neoplasms in the urogenous tract. As the rapid development of the chemical industry and the continuous production of new chemicals makes it impossible to devise on the basis of individual chemicals a compensation law not only adequate for existing conditions, but flexible enough to include future situations, the best solution of this perplexing problem is offered by the blanket laws passed in several states (Wisconsin, New York, California, Connecticut, North Dakota, Illinois, Massachusetts, Missouri). Such a law includes automatically not only the dye intermediates (benzol and naphthalene derivatives), but also certain azo-dyes (sudan III, etc.), among the substances for which adequate evidence of their carcinogenic effect upon the urogenous organs is available (Hibbs).

As an illustration of the legal complications which may arise from compensation laws naming certain chemicals as recognized causes of aniline tumors, the laws of Switzerland and New Jersey may be cited (International Labour Conference). The laws of both states recognize only amino-derivatives of benzol as causative agents of bladder tumors. Through this inadequate word-

ing of the law vesical neoplasms caused by the occupational exposure to amino-derivatives of naphthalene (naphthylamine) are not included in the compensation legislation. In Switzerland, fortunately, the industrial commission possesses the authority to grant compensation in all cases for which an occupational genesis can be demonstrated. It is through this clause that the Swiss dye workers with bladder tumors following exposure to naphthylamine obtain compensation (Barkmeyer). The laws of New Jersey do not provide for such eventualities.

Because of the uncertainty still existing in regard to the minimum time required and the conditions necessary to elicit a neoplastic response in the bladder of dye workers subsequent to the exposure to aromatic amines, the following directions, representing a modification of some proposals made by Scheele, may serve as a guide in making medico-legal decisions concerning the occupational chemical genesis of urogenous tumors in persons claiming compensation:

1. An interrelation between tumor formation and occupation exists, with the highest degree of probability in persons employed in the production and handling of aniline, benzidine, naphthylamine and their isomers, homologues and derivatives, when at least two years have passed between the beginning of employment and the appearance of bladder tumors. The occurrence of any attacks of acute poisoning indicated by the presence of hematuria, strangury, cyanosis, etc., is not essential for the establishment of this interrelation.

2. The probability of an exposure to aromatic amines with carcinogenic qualities must be assumed in all persons who work or live in close proximity to establishments where these compounds are produced or handled (environmental dust and fume zone).

3. The possibility of an etiological connection between the development of bladder tumors and exposure to aromatic amines exists also in cases which occur among the population living or working in the vicinity of the factory district, if it can be shown that the disposal of fumes and dust in the production and handling of these compounds within the factory is inadequate, resulting thereby in contamination of the environmental air with carcinogenic substances.

4. Causative relations may be present also for workers who use or handle free aromatic amines as mordants in the dyeing of leather, textiles or as accelerators or vulcanizers of rubber. Symptoms of acute poisoning here are not essential requirements for the establishment of a carcinogenic action. Only the repeated and chronic effect of aromatic amines can be here considered.

5. Small probability of a causative connection between aromatic amine effect and tumor formation exists, when finished products (dyes) are handled. Such claims should be allowed if it can be shown that the particular dye or dyes

contain aromatic amines as impurities, or may decompose in the body into carcinogenic degradation products of aromatic amine character, or exhibit a neoplastic action upon the urogenous tract in experimental animals.

6. Tumors which develop under the above stated conditions may occur in the kidney, renal pelvis, ureter, urinary bladder or posterior urethra. The time of occupational exposure to these aromatic amines and dyes should not be less than one year. The latency period may be up to forty years.

XVIII. SOCIAL ASPECTS

Aniline tumors of the urogenous organs are of distinct social significance for several reasons.

1. It is of definite and direct social importance that members of a certain occupational group are affected by neoplastic conditions which may cause prolonged disability and which may result not infrequently in death. Apart from the moral and mental effects produced by such an industrial disease upon the person involved and his dependents, disorders of this type will affect seriously the economical status of these persons. While these financial effects are somewhat mitigated in states with adequate compensation laws, the absence of such legal provisions removes, as a rule, the last protective barrier from a severe economical calamity, as the persons affected in the great majority of instances belong to the financially weak laboring class. The diseased worker and members of his family are apt to become public charges. The existence of this industrial neoplastic disease is a public financial and moral liability, which a community should be anxious to keep as low as possible.

2. The social interest in this industrial disease should be especially keen in those communities which have in their midst chemical factories producing or handling aromatic amines, in view of the possibility that even persons not employed in these establishments, but living within their environmental fume zone, may be affected by aniline tumors, if the methods of production are controlled inadequately. It is necessary that local health authorities devote proper attention to these possibilities and take the necessary steps to protect the population wherever plants are negligent in the proper disposal of fumes and dust containing carcinogenic aromatic amines.

3. In an editorial, *Industrial Medicine* (1933) emphasizes that the manufacture of aniline dyes requires careful technical and medical supervision so as to guard the health of workers exposed to hazards connected with the various manufacturing processes involved. It seems desirable that the introduction and observation of pertinent technical and medical preventive and protective measures is not left to a large extent to individual initiative and discretion, but that certain minimum requirements be fixed by law and enforced by governmental factory inspectors. Such laws would protect the legitimate interests of the community. This special factory supervision should be ex-

tended to dye works, dyeing establishments, explosive manufacturing plants, perfumery and soap factories, rubber factories and manufacturing establishments of the chemical and pharmaceutical industry.

4. The demonstration of the carcinogenic urogenous action of certain dyes is an additional factor of general social significance. Serious consideration should be given to a proposal recently made by Maisin, who suggested that all dyes exhibiting such properties should be prohibited for use as coloring matter of chocolates, candies, pastries, lemonades, cosmetics, medicines, foodstuffs and wearing apparel, thereby eliminating any repeated and prolonged introduction of these dyes through the skin, alimentary and respiratory tract.

3. CARCINOMA OF THE URINARY BLADDER IN OCCUPATIONAL VESICAL SCHISTOSOMIASIS

I. HISTORICAL ASPECTS

Bilharziasis or schistosomiasis of the human urinary bladder, in all probability, is the oldest occupational disease possessing neoplastic potentialities. The knowledge of this parasitic disease, most prevalent in Egypt, is as old as the history of that country, 5th dynasty, 3160-2920 B.C. (Carozzi). It is mentioned in the papyri of ancient Egypt because of the high incidence of hematuria brought about by this helminthic infection among the fellahs. While it has not been possible to demonstrate actually the parasites, or their ova, in the bladder of mummies dating from those times, since this organ as well as the rectum was removed during the mummifying process, Ibrahim reported that Ruffer discovered ova of Schistosoma haematobium in the renal cortex of three mummies dating from 1250 to 1000 B.C. This proves definitely the occurrence of this infection among the inhabitants of ancient Egypt. However, it was not until three thousand years later that the existence of a causative interrelation between this parasitic vesical infection and the development of benign and malignant bladder tumors was suspected (Fenwick, Kartulis) and shortly afterwards established definitely (Goebel, Ferguson).

II. CAUSATIVE AGENT

Of the three species of blood flukes (Schistosoma haematobium, Schistosoma mansoni, Schistosoma japonicum) which parasitize large groups of human population, Schistosoma haematobium and mansoni invade the tissues of the urinary bladder. The vesical infection with Schistosoma haematobium, however, is by far the more frequent and extensive of the two and, in general, considered as the chief or sole cause of secondary, neoplastic vesical lesions. Schistosomiasis of the bladder is prevalent in Egypt, Sudan, the countries of northern, eastern and southern Africa (Morocco, Somaliland, Madagascar, Transvaal, etc.) and regions of Asia west of the Indus River (Syria, Mesopotamia, Palestine, India). Southern Portugal harbors the disease endemically,

and isolated cases have been reported from the Isle of Cypre and from Greece.

Schistosoma haematobium (Distomum or Bilharzia hematobia) is a trematode, the male worm being 12-14 cm. long and 1 mm. wide, while the female is 20 mm. long and 0.25 mm. wide. The female is carried in the gynecophoral canal of the male. The larval forms (cercariae) of this worm are free living, swim in the water and, upon contact with the skin or oral mucous membranes of man, penetrate the epithelial lining and invade the peripheral venules. From there they are transported to the right heart, pass then through the pulmonary capillaries in the course of a few days and are carried into the general circulation. While the great majority of cercariae present in the circulating blood die, those which are shunted into the mesenteric arteries pass through the mesenteric capillaries and venules and become finally lodged in the portal venous network. In the hepatic portion of the portal system the cercariae grow and undergo sexual differentiation, becoming thus mature worms. After having attained this developmental stage, the worms move against the direction of the blood stream into the inferior mesenteric veins and invade the venous plexus of the pelvis, especially those adjacent to the urinary bladder, but to a lesser extent also those of the rectum. Following sexual maturation in this location, the female worms deposit over an extended period their eggs in the fine venules and capillaries of the bladder, rectum and adjacent organs, such as prostate gland, ureter, vagina, uterine cervix, colon, and appendix. Many of the ova remain at the site of deposition, while others are carried back into the portal system or into the inferior cava vein and may thus reach remote organs, such as the lungs, kidney, skin, brain, etc.

The eggs, which are oval in shape and measure 112 to 170 microns by 40 to 70 microns, possess a terminal spine and are almost mature when laid. A chitinous capsule surrounds an embryo (miracidium), which produces a lytic agent, which penetrates the capsule and enables the ova with the help of the spine to penetrate the mucosa of the urinary bladder and of the rectum, reaching thus the lumina of these organs and being finally excreted with the urine and feces. Many of the ova, however, remain where deposited and ultimately die becoming subsequently calcified. The great majority of the ova which succeed in entering the vesical cavity are viable and hatch soon after being excreted into a watery environment. The miracidiae escape from the chitinous capsules as free swimming forms. Their further development depends upon the presence of a certain species of fresh-water snails (Bulinus truncatus in Egypt; planorbis duforii in Portugal and Morocco, etc.). When contacting these snails, the miracidiae invade them and undergo in the liver of these molluscs in four to eight weeks a metamorphosis into the larval form (cercariae) after having passed through two generations of sporocysts. The cercariae leave the snail and swim free in the water. Their body is ovoid, measuring 140 to 240 microns in length and 57 to 100 microns in width, and possessing a large anterior and small ventral sucker. The tail is 175 to

250 microns long and 35 to 50 microns wide, and consists of a trunk and a pair of caudal furci (60 to 100 microns long) (Craig and Faust). The cercariae may become attached for some time to the surface film of stagnant or slowly flowing water, and it is here that they make contact, most commonly, with man while bathing or removing water to be used for bathing or drinking purposes. When the infectious water evaporates on the skin, the cercariae contained in it shed their tails and invade the skin. The ova of Schistosoma haematobium are, on the other hand, not infectious for man.

III. CONDITIONS OF EXPOSURE

The description of the life cycle of Schistosoma haematobium indicates that the presence of water and the thereon depending existence of the water snail, forming the intermediary host, is the essential requisite for the production of this vesical disease in man. It is therefore readily understandable that the conditions present for many centuries in Egypt, especially Lower Egypt and the delta district of the Nile, furnish a particularly favorable environment for the existence of this malady, as the yearly inundations of the Nile valley supply the necessary wet medium for the survival of the snails and thus also of the cercariae, while the agricultural methods practised and the habits observed by the inhabitants of this country facilitate the infection with the cercariae and the continuous infestation of the water with miracidiae. The various factors which favor the spread of the disease and which are responsible for its perpetuation through the ages have been vividly described by Ibrahim, as follows:

1. The Egyptian farmers (fellahs) work barefooted in the fields, where they are usually ankle deep in slush and water, which are heavily infested with cercariae that penetrate the skin of the ankle and thus gain access to the body.

2. The fellahs drink the infected water as the hot climate makes them very thirsty during work. The cercariae thus imbibed penetrate the mucous membrane of the buccal cavity, which represents the second port of entrance of the infection.

3. After defecation and urination, as well as four to five times a day before prayer, the fellahs wash themselves with the infected water. Every time before prayer they rinse their mouths and nasal cavities three times with the water at hand, which is usually infected when coming from the small canals or draining ditches, and wash their faces, arms and feet. These ablutions, demanded by their Mohammedan religion, increase considerably the opportunities of infection.

4. Bathing in the canals, which is a great relief to the overworked fellahs in the hot weather as well as a common form of sport among the village boys, furnishes additional chances of contact with the cercariae and is responsible for the generalized occurrence of schistosomiasis among the members of younger age groups, especially in rural districts.

5. The religious demands for ablutions after defecation and urination entice the fellahs to drop their excreta containing the ova on the banks of canals and drains or directly into the water of them, where it is handy for the ablutions required afterward. The ova are thus placed directly into the ideal medium for further propagation of the maximum number of cercariae, as these organisms would readily die when left in a dry spot exposed to the action of the intense heat and strong actinic rays.

6. An important role in perpetuation of the disease is due the methods of cultivation of the soil, as these determine the degree and duration of its moisture. Two methods of irrigation are practised in Egypt: the ancient or basin method and the modern or canal-and-drain method. With the ancient method, the water of the Nile, which begins to rise in June, is permitted to flood the fields in August when it reaches its highest level. In October, the water is allowed to drain back into the Nile. Seeds are then simply thrown over the surface and a sort of wooden raft is passed over to smoothen the surface and to mix the seeds with the superficial soil. The farmer waits from then on for the harvest until the next April. During the early summer the intense heat dries the soil so completely that the snails, left in the former wet slush covering the ground, die. The number of infected or potential hosts for the cercariae is thus considerably diminished every year. Districts cultivated according to this system, which permits, however, only one crop a year, show a relatively low incidence of infections among the fellahs (20 per cent).

The modern method of cultivation, which was introduced about 100 years ago and is spreading constantly, permits a continuous irrigation of the fields by way of irrigation canals fed from bodies of water accumulated behind dams and barrages built into the Nile. In the waters of the canals and drains, and in the vegetation of their shores, the snails thrive and thus furnish necessary and ample hosts for the cercariae throughout the entire year. The incidence of schistosomiasis among the farming population (men, women and children engaged in agricultural work) is very high (85 per cent) for this reason. While permitting the harvesting of several crops per year and thereby aiding the material prosperity of the country at large, this system has undermined the health of the farmers, as it has not only favored the spread of schistosomiasis, but also the dissemination of ankylostomiasis, dysentery and malaria (Scott).

IV. INCIDENCE

The incidence of vesical bilharziosis among the Egyptians is generally high, but varies in degree in different parts of the country depending upon geological formation and the agricultural methods used. The disease is more common in Lower Egypt than in Upper Egypt. It affects mainly the rural population, and especially those engaged in farming. It has been stated that about 70 to 90 per cent of the population of Egypt is infected with Schistosoma, that

is, 9 to 10 million people out of a total of 13 million inhabitants (Diamantis; Ibrahim; Pfister; Khalil; Scott; and others). The disease is less common among the urban population (54 per cent of artisans and proprietors are infected (Ibrahim)), than among the people inhabiting the countryside (85 per cent of agricultural workers (Ibrahim)). The infection with Schistosoma haematobium is not infrequently associated with an infestation by Schistosoma mansoni which deposits its eggs chiefly in the capillary network of the rectum and colon and only to a minor degree in that of the bladder. Infections with Schistosoma mansoni were present, according to Ibrahim, in 51 per cent of the agricultural class and 8.7 per cent of the urban group of the same locality investigated as to the incidence of Schistosoma haematobium infestations.

All observers agree that the great majority of persons afflicted with schistosomiasis does not develop vesical neoplasia. According to an estimate of Dolbey and Mooro, the incidence figure of vesical cancer in vesical schistosomiasis is one case of cancer in one thousand six hundred cases of clinical schistosomiasis. As these investigators do not state the method by which they arrived at this figure, it represents apparently a matter of optimistic conjecture, because the frequency of vesical cancer associated with Bilharziasis is found to be many times higher from observations made at autopsy on persons who succumbed to their parasitic infection. Kartulis found 11 vesical neoplasms among 300 cases of bilharziosis autoptically examined (4 per cent). A similar figure of incidence was recorded by Goebel (5 per cent). Data available as to the number of vesical Bilharzia cancers among the total number of malignant neoplasms observed in Egypt, moreover, indicate quite clearly that this tumor represents one of the major types of cancers in that country (Pfister: 20 per cent of total number of cancers were Bilharzia tumors of bladder; Dolbey and Mooro: 7.6 per cent (51 vesical cancers among total of 671 cancers examined) were Bilharzia cancers (2 to 3 per cent of all cancers in Europe and the United States are bladder cancers)).

Bilharzia cancer of the bladder is apparently much more prevalent among males than females, as so far only two cases of this neoplasm have been found in women (Ferguson; Diamantis (two in fifty cases against one in four in cryptogenetic vesical carcinoma)). The reason for this difference is attributed by Ferguson to a fundamentally different behaviour of the female bladder in infestation with Schistosoma haematobium, in comparison to that present in males.

V. AGE

Inasmuch as the first infection with Bilharzia takes place usually during childhood as the result of bathing in or drinking of infected water, the vesical tumors make their appearance at an earlier age (30 to 40 years (Diamantis)) than that observed with the cryptogenetic type of bladder cancer (50 to 60

years). The occurrence of a bladder carcinoma in coexistence with a vesical schistosomiasis in a fellah 14 years old was reported by Kartulis. The occupational Bilharzia tumor of the urinary bladder conforms in this respect to the behaviour displayed by occupational cancers in general, that is, the duration of exposure determines the time of manifestation without regard to the absolute age of the person afflicted.

VI. SYMPTOMATOLOGY

The early symptoms, following several days after the invasion of the worms, are characterized by fever, malaise, general muscular pain, and a more or less generalized urticarial rash. There exist a leucocytosis and marked eosinophilia (up to 50 per cent and more) of the blood. These acute toxic symptoms are caused by substances eliminated by the juvenile and adult worms, as similar manifestations can be experimentally reproduced in animals artificially infected with large amounts of these trematodes (Hutchison). Several months later urinary disturbances make their first appearance, consisting in hematuria at the end of micturition. This symptom may disappear spontaneously and the infected person may remain symptom-free over a period of several years, until such time when the progressive development of chronic vesical lesions results in a reappearance of urinary manifestations, such as hematuria, dull pain in the bladder region and groins, pollakiuria, nocturia, burning sensation at the time of and after urination, etc. With the gradually increasing pathologic changes of the bladder wall, difficulties in urination ensue, as the bladder becomes of limited capacity and unable to contract. As the result of obstructive and destructive processes in the urethra, elephantiasis of the penis and urethral fistulas into the scrotum and perineum may develop. The infectious, inflammatory lesions may spread ascendingly into the wall of the ureter and kidney and thus cause an ureteritis and pyelitis. Secondary bacterial infections of the bladder are frequent during this stage. The urine contains a leucocytic sediment with a predominance of the eosinophilic cells (up to 80 per cent) and ova of S. haematobium. These are mainly present in the last portion of urine. The urine has usually an acid reaction, unless a secondary bacterial infection exists, which may cause an alkaline urine. The prostate gland is more or less considerably enlarged.

In addition to these symptoms from the urogenous organs, there exist, usually, more or less serious parasitic complications in other organs. A hypertrophic and less often an atrophic cirrhosis of the liver exists during a more advanced stage in many cases, especially in young adults (Kartulis; Symmers), as a reaction to the presence of ova in the portal system. Multiple pseudo-tubercular foci are not infrequently observed in the lungs caused in response to the toxic substances released by degenerating parasitic ova located in the vascular lumina, resulting in vascular obliteration with clinical symptoms similar to those observed in Ayerza's disease (Shaw and Ghareeb;

Mainzer). The spleen is often enlarged and contains a pigment resembling that found in malaria and similar to that existing in the enteric tract of the worms (Hutchison). A marked involvement of the cervix and vagina may occur in women and may finally lead to a cicatricial constriction of the vaginal canal, following a preceding thickening and wrinkling of the vaginal mucosa with the appearance of a widespread verrucosis, complicated by abscess and scar formation (Hutchison). A marked eosinophilia is found in the blood. While the serum of infected persons gives, during the later stages, a positive complement fixation test with the liver extract from infected snails (Fairley), there does not develop any appreciable degree of immunity against the infectious agent, even in the presence of a prolonged or repeated parasitic infestation.

VII. PATHOLOGY

The cystoscopic examination performed during an early stage of a vesical schistosomiasis shows an inflamed and hyperplastic vesical mucosa, with dilated submucosal veins. This change is present in the entire bladder, but especially marked in the trigonal and paratrigonal region and in the posterior wall of the bladder as well as the posterior portion of the urethra. The prostate gland is swollen and indurated. When a massive infestation of the bladder wall with parasitic ova exists, there occurs a diffuse thickening of the mucosa without the formation of localized polypous mucosal projections. These rather plump, localized, inflammatory, mucosal and submucosal reactions, which make their first appearance at a relatively early stage, consist of a vascular inflammatory granulation tissue and are most frequently located and most numerous in the lower segment and posterior wall of the bladder. Coincidental with the extrusion of the parasitic eggs through the vesical mucosa, parts of this tissue may slough and the defects may be covered by mineral precipitations (phosphates) from the urine. Scaled off fragments of these mineral crusts may form together with necrotic eggs and clotted blood, the nucleus of calculi which grow by the superficial deposition of oxalate and uric acid crystals. Leukoplakias are frequently found during this stage in the vesical mucosa. During the further course of the disease, the vesical lumen shrinks and the walls become increasingly rigid. Secondary bacterial infections contribute to and aggravate the inflammatory reactions in the bladder wall, causing the development of abscesses and fistulas. The spreading of these processes upon the posterior urethra may cause a clogging of the urethral lumen, due to mucosal swelling and thickening and the lodging of larger particles of necrotic matter expelled from the bladder into the urethra. Similar inflammatory changes develop in the ureters and renal pelvis when the infection spreads in a retrograde direction.

The pathologic vesical lesions described furnish the soil from which papillomas and cancers may develop in the bladder and also occasionally in the

ureter and renal pelvis. In addition to tumor formation in these urogenous organs, schistosomiasis has been incriminated for the production of a papilloma of the clitoris, a melanosarcoma of the rectum (Diamantis), several adenocarcinomas of the rectum, colon and appendix (Hutchison) and a considerable number of primary carcinomas of the liver (Pirie).

The chief location of the Bilharzia tumors of the bladder is the trigonal and paratrigonal region (ureteral orifices and internal urethral os), and the posterior wall, while the anterior wall is rarely the site of a parasitic neoplasm. Carcinosis of the entire viscus is occasionally observed. Benign papillomas, which represent the less frequent type of Bilharzia neoplasia of the bladder, are usually rather plump, polypous formations. Malignant manifestations may also exhibit a papillomatous or cauliflower-like appearance, but the majority of these blastomas are nodular or flat and infiltrative masses, not infrequently partly or completely covered by mineral incrustations. Multiplicity of tumors is the rule and not infrequently the bladder is studded with neoplasms ranging from lentil to apple size.

The histologic examination of the bladder wall undertaken at various stages of the preneoplastic period reveals a great variety of changes. The deposition of ova in the capillaries and venules of the submucosa and muscularis of the bladder is followed by the development of a perivascular eosinophilic-leucocytic exudate. The affected and dilated vessels show often, but not always, subsequently endophlebitic and periphlebitic productive changes with endothelial proliferations which may lead to thrombosis and vascular obliteration. Whereas the escape of ova from the bladder wall is usually accompanied by the production of mucosal ulcers, their retention in the vesical tissue is, in general, followed by the appearance of pseudotubercular formations with multinucleated giant cells of foreign body type around the ova which ultimately became calcified. It is of importance to note that these inflammatory changes involve the bladder in its entirety (pancystitis) and do not only affect the mucosa and submucosa. With the increasing duration of this inflammatory status, the vesical tissues become more and more fibrotic and lose thereby their contractile qualities.

In spite of the fact that the neoplastic manifestations that develop not infrequently in a relatively large group of people on the basis of pathologic changes described above have been known for several decades, only relatively meager information exists as to their detailed histologic structure and practically no information has been placed on record that concerns the precarcinomatous histologic changes of the bladder mucosa and submucosa. Apparently no attempt has been made to approach this important problem experimentally by studying the pathologic manifestations and reactions in the monkeys (cercocebus fuliginosus) which are naturally susceptible to the causative agent, Schistosoma haematobium.

The following information concerning the histologic structure of Bilharzia tumors of the bladder is available: The papillomas have a delicate, markedly vascular stroma infiltrated with eosinophilic leucocytes. The malignant blastomas observed are mainly carcinomas, but an appreciable minority possess a sarcomatous morphology (Ferguson: 34 carcinomas and 6 sarcomas; Kartulis: 9 carcinomas and 1 sarcoma; Hutchison: among many carcinomas, several sarcomas; Dolbey and Mooro: among 51 vesical tumors, several sarcomas). The incidence of sarcomas is about 14 per cent in the Bilharzia series, while only 4 per cent of cryptogenetic bladder cancers are sarcomas. The majority of the carcinomas are cornified squamous cell carcinomas, others are of the transitional cell type or show a glandular structure (Goebel: 11 squamous cell carcinomas, 6 transitional cell carcinomas, 2 adenocarcinomas). This numerical distribution of the carcinomas according to the morphologic structure is in striking contrast to that existing in the cryptogenetic vesical carcinomas, which show a predominance of the transitional cell carcinomas, while the cornified squamous cell carcinomas and adenocarcinomas are relatively rare. A classification on the basis of the parenchyma-stroma relation is proposed by Diamantis: 1) A scirrhus type consists of irregular islands and columns of epithelial cells embedded in a fibrous tissue containing numerous viable-looking ova, which are not surrounded as usual by giant cells, monocytes and eosinophilic cells. 2) A soft cellular carcinoma, with hardly any stroma and only thin delicately walled blood vessels, contains a few ova amidst cancer cells and a few calcified ova in the adjacent submucosa. 3) A common variety of cornified squamous cell carcinoma shows many calcified ova especially near the base of the tumor with a few ova embedded in the epithelium; the ova are surrounded by eosinophilic cells, but not by giant cells.

The distribution and number of ova in these tumors varies considerably with the individual neoplasm. They may be diffusely distributed or occur in clusters. They may vary in number in different parts within a particular tumor and may sometimes involve only the marginal portions of a tumor. Ova occur within the stroma as well as in the parenchyma. Sometimes, apparently, they are carried along with the mobilized tumor cells and are included in the formation of secondary deposits (Pfister).

The malignant tumors exhibit a marked tendency to invade by continuity the adjacent organs (prostate, rectum, seminal vesicles) and to penetrate into the lumen of the blood vessels. This last mentioned fact may account for the relatively high incidence with which metastases are found in the right heart (Ferguson: in two out of five cases studied at autopsy), an occurrence, rarely observed in cryptogenetic bladder tumors. Metastases in general are more frequent in Bilharzia cancers than in cryptogenetic cancers and may involve the regionary lymph nodes as well as remote organs (lung).

VIII. CAUSATIVE MECHANISM

During the early years following the discovery of interrelations between the vesical schistosomiasis and epithelial overgrowth of the bladder mucosa, the actual malignant character of these proliferative manifestations was not always recognized. Fabre-Doumergue contended in 1898 that the epithelial proliferations were not genuine carcinomas, but represented merely epithelial thickenings resulting in the development of an "epitheliomatosis" of the bladder mucosa unrelated to cancer. A similar opinion was held by Wolff in 1907. The demonstration of invasive growth into the adjacent organs, as well as of metastases to remote organs (Ferguson), did not leave any doubt that these cellular overgrowths of the bladder were malignant neoplasms. The controversy in regard to these tumors has revolved from then on mainly around the question, whether these cancers were the result of a direct specific or nonspecific action of metabolites or degradation products of the worms or their ova, or represented simply the ultimate outcome of a nonspecific secondary chronic irritation of the bladder tissues in which non-parasitic factors played the main role.

A direct specific carcinogenic action of the worms upon the bladder mucosa is regarded as the cause of the vesical tumors by Lewin as well as by Albarran and Bernard. A similar conception is apparently held by Pfister and Diamantis, as both investigators claim that the cancerization of the bladder depended upon a repeated infestation with Schistosoma haematobium. Diamantis, however, adds a modifying provision by stating that the reinfection must act upon a bladder containing calcified ova, being evidence of a schistosomiasis of long standing. The alleged absence of Bilharzia cancer of the bladder in Europeans is explained by Pfister with the contention that reinfections, which are in his opinion essential for vesical cancerigenesis, do not occur among Europeans. This reinfection theory of Diamantis and Pfister is directly contradicted by a statement of Hueckel, who asserts that a Bilharzia cancer of the bladder may follow upon a single infection. While the existence of a specific carcinogenic metabolic or degenerative parasitic product is a matter of pure speculation, there exists reliable evidence supporting the contention that the worms as well as the ova exert a direct injurious effect upon the tissue adjacent to them. Clinical as well as experimental evidence indicates that the live worms excrete or secrete a toxic substance causing generalized systemic disturbances. Whether these products are capable of producing localized cellular damage near the worms is doubtful, however, if credence can be given to a statement of Shaw and Ghareeb, who claim that the live worms located in the pulmonary vascular system are innocuous, while the dead worms give off a highly toxic product causing vascular necrosis and localized pneumonia.

The action of the live ova on surrounding tissue is mechanical as well as

chemical in nature. The spine may cause a repeated cellular mechanical trauma by participating in the movements of the bladder wall caused by its contraction and distension. The lytic substance allegedly secreted by the miracidia may be responsible for the development of the acute inflammatory reaction around many of the ova. It seems also to be possible that the dying and dead ova may give off toxic degradation substances, but it is scarcely conceivable that the calcified ova represent anything else than calcified foreign bodies possessing no other specific chemical property.

A nonspecific irritative action of the eggs upon the bladder wall in general, and on the vesical mucosa in particular, is the cause of the carcinogenesis in this organ in the opinion of Goebel and Ferguson. Ferguson calls the Bilharzia vesical cancer the irritation cancer of Egypt. This conception finds the approval of Oberndorfer, who points out that the eggs can scarcely exert a stimulating effect upon the proliferative properties of the epithelial mucosa of the bladder.

A carcinogenesis unrelated to the parasitic infection, but depending upon the presence of an inflamed septic bladder containing an alkaline urine is the conception advanced by Dolbey and Mooro. These investigators point out in support of their theory that the incidence of parasitic disease in the renal pelvis, ureter and intestinal tract is almost as great as in the bladder, and yet the development of cancer on the basis of the bilharziasis in these organs is almost unknown. They believe that the acid reaction present in the intestinal tract plays an important role in preventing a cancerous response. The emphasis which Dolbey and Mooro placed upon the etiologic role of the alkaline reaction of the urine has not remained undisputed, as Diamantis found that the urine in vesical schistosomiasis and cancer is not alkaline during the early stages as long as no complicating bacterial infection is present.

An entirely different explanation as to the causative carcinogenic mechanism present in schistosomiasis is proposed by Borrel who maintains that the parasites may be the carriers or hosts of a carcinogenic virus. It may finally be mentioned that Schrumpf-Pierron doubts the occurrence of true metastases of the vesical neoplasms, but asserts that the multiple extravesical blastomatous foci represent independent cancerigenic tissue responses to the presence of ova at these sites.

It is readily apparent from an analysis of the evidence presented that none of the various theories and conceptions cited above offers a satisfactory explanation of the causative mechanism active in the production of Bilharzia tumors of the urinary bladder. While it cannot be doubted that this parasitic infection plays an important and definite role in eliciting the neoplastic vesical response, a great deal of uncertainty surrounds the character of this role from a local as well as systemic standpoint. The fact that only a rather small percentage of persons dying with vesical schistosomiasis show the presence of bladder tumors has been interpreted as evidence that the infec-

tion alone was only one of the factors involved, but not sufficient to cause cancer. It is my opinion that this sort of reasoning is not entirely convincing as long as data are not available on the duration and severity of the vesical infection in the cancer positive and negative cases, as it has been shown that at least in the experimental production of parasitic liver tumors, this factor plays a definite role in determining the incidence and occurrence of these neoplasms in the liver of rats.

There exists, however, circumstantial evidence which throws some serious doubts on a direct and chief causative role of the parasites located in the bladder. In spite of the fact that pulmonary schistosomiasis is not a rare occurrence, this condition has so far never given rise to the development of a pulmonary tumor, although it results in circulatory disturbances which are considered by some investigators as a fundamental cause of malignant neoplastic growth (chronic impairment of the blood supply). To this it may be added that the incidence of intestinal Bilharzia carcinoma is negligible when compared with the high frequency of Bilharzia papillomatosis of this organ, and that there is a great rarity of intestinal cancer in general among the inhabitants of Egypt (Dolbey and Mooro). The predominant occurrence of the Bilharzia tumors in the dependent and posterior parts of the bladder, that is, in locations identical with those of the cryptogenetic tumors, suggests that not the intravascularly located parasites or their ova, but some unknown nonparasitic agent plays apparently an important role in determining the site as well as the character of the proliferative epithelial response. It is scarcely conceivable that this part should be assumed by a hypothetical virus harbored by the worms, as no such tissue response is observed in other locations in most instances and does not represent even in the bladder a constant occurrence.

The conception of a significant etiologic role of a nonspecific chronic irritation of the bladder mucosa may be dismissed not only on general grounds as unsatisfactory, but can be disregarded because the chronic cystitis with stagnant urine so often existing in old men with hypertrophy of the prostate gland as well as with old women with a cystocele on account of a uterine prolapse, does not show any excessive tendency toward vesical cancer. The etiologic role of a chronic mechanical traumatization of the bladder tissue by the ova and their spines can also be discountenanced, as chronic mechanical trauma is scarcely ever the direct and main cause of any cancer. The remarkable rarity of cancer of the uterine cervix in completely prolapsed uteri, in which the cervix is exposed in the vulva not only to a continuous chemical irritation from urine and feces, but also to various kinds of mechanical injury, such as friction, etc., should discourage any attempt to attach any appreciable weight to this factor.

Every one of the theories cited focuses its entire attention upon the pathologic conditions present in the bladder. None gives any consideration to the fact that schistosomiasis is a disease affecting several organs in addition to the bladder, which may very well exert a definite influence upon the

proliferative reactions occurring in this viscus. It is pertinent to recall the frequent presence of cirrhosis of the liver in schistosomiasis, especially in younger persons, that is, in that age group which is most often affected by cancer of the bladder. While no data are available from Egypt which would indicate that this hepatic condition may have led to the development of hepatocarcinomas, Pirie has published a series of cases in which infections of Schistosoma haematobium were considered the cause of cirrhosis and subsequent hepatocarcinoma of the liver in young South African Negroes. It is remarkable, that vesical schistosomiasis and cancer were, on the other hand, apparently not observed in South Africa. As carcinomas have been observed in three organs (liver, intestine, bladder) of persons affected with chronic schistosomiasis, and as these three organs come in intimate contact with the metabolites (normal and pathologic) of the liver, it does not appear to be too far fetched to reflect upon the possibility of a causative relation of these products to the appearance of malignant tumors in these three organs. The parasitic infection and inflammation would take over in this process the role of a nonspecific conditioning and sensitizing agent, by causing local changes in the cellular permeability and reactivity of the epithelial cells and in the conditions of their vascular blood supply.

IX. PROGNOSIS

The ultimate prognosis of vesical schistosomiasis and to a still higher degree that of Bilharzia vesical cancer is unfavorable without treatment. Death is usually caused by urogenous sepsis. The prognosis of the parasitic infection, when made early enough, that is, before too severe tissue damage has occurred, and properly treated, is good. Injections of sodium antimony tartrate or fouadin are almost specific means to combat the disease. Bilharzia carcinoma offers, on the other hand, even when discovered relatively early and treated adequately, an unfavorable prognosis on account of the complicating pancystitic conditions prevailing in the bladder wall.

X. PREVENTIVE MEASURES

Various methods have been tried or have been proposed for the control of this important parasitic disease in Egypt. An extensive chemotherapeutic campaign, such as suggested by Ibrahim and undertaken apparently some time ago, proved to be unsuccessful (Craig and Faust). Such a measure must be considered as a hopeless task because even at best only a part of the eggs will be killed by such measures, as not all persons affected can be apprehended and subjected to the necessary course of treatments, while the sources of infection, the water of the canals and drains, will provide an opportunity for constant re-exposure.

In a second proposal Ibrahim considered the possibility to supply villages with uncontaminated water from springs and from the large canals, the

water of which usually does not contain any cercariae on account of the swift current. This plan had also to be discarded as such a measure would not help the fellahs working in the fields where they have no access to these sources of pure water, but would be forced to continue the use of infected water. Similar objections were raised by Ibrahim against the construction of special sanitary latrines in the villages for the disposal of the excreta containing the eggs. The argument advanced in favor of this plan was that by the destruction of the ova contained in the excreta the vicious circle responsible for the perpetuation of the infection would be interrupted. Again such a measure would not provide for the fellah working in fields far from these special latrines. It may be said that any plan which relies for its success upon the intelligent and spontaneous cooperation of the fellahs is probably doomed to failure, as about 80 per cent of the Egyptian population is illiterate and therefore not easily amenable to ordinary means of education in matters of personal hygiene and, moreover, has acquired certain customs objectionable for hygienic reasons, but deeply rooted in the religious life of these people.

It is for this reason that the following two measures proposed by Ibrahim seem to possess greater merits than those cited above. Ibrahim suggested to spray a dilute copper sulfate solution on the fields, as this chemical would kill the snails without harming the vegetation. This method was regarded as especially suitable for the treatment of rice fields. It is, however, evident, that such a procedure has its distinct limitations in regard to general application as well as efficacy, and is apparently best suited as an auxiliary measure to be used in support of and in addition to the second plan proposed by Ibrahim. This was thought by Ibrahim to represent the most effective means to combat the infection. The country was to be divided, according to this scheme, into four districts, in one of which each year the irrigation would be discontinued during the hot summer months, so that the soil would be thoroughly dried and thus the snails be destroyed, thereby removing an important and essential link in the life chain of the infection. By applying this measure in rotation to the four districts, a certain amount of control would be achieved without imposing too great an economical hardship on the proprietors and agricultural workers, as they would have to reduce only every fourth year the number of crops to a single one. It is obvious that an effective check of the sources of infection will bring about a reduction in the number of infections and reinfections, and will thereby contribute to the control of conditions reponsible for the production of Bilharzia carcinoma of the urinary bladder.

XI. INFECTIOUS PAPILLOMATOSIS OF THE URINARY BLADDER IN RATS

The occurrence of the epithelial papillomatosis of the urinary bladder of rats provides not only an interesting phenomenon of parallelism in etiologic and morphologic respects to the parasitic neoplasia of the bladder in man, but it is of even greater importance by reason of the relation existing between

the location of the causative agent in regard to site and type of proliferating epithelial cells. The infectious papillomatosis of the bladder of rats is caused by an infestation of the transitional epithelial lining of the bladder, ureter and renal pelvis with a worm, trichosomoides crassicaudans and its eggs. Apart from the occurrence of these organisms free in the lumen of the bladder, they appear as intraepithelial inclusions in the lining, causing localized thickenings of the epithelial mucosa usually associated with the formation of solid epithelial papillary projections. The papillomatosis becomes, occasionally, very extensive and marked, resulting in the merger of the individual papillomas into an adenomatoid spongy network filling the lumen of the bladder. A connective tissue stroma is found only in very large and advanced papillomata. The condition is rarely associated with any inflammatory reaction in the submucosa. The disease is frequently seen in the domesticated albino rat and has been described by several investigators (Watanabe; Löwenstein; Fibiger; Jaffé and Radt; Hückel; and others). The author has found it in about 80 per cent of a series of approximately 2,000 rats.

The significance of this proliferative manifestation in relation to the Bilharzia vesical carcinoma of men lies in the fact, that these papillomas in the rat do not show at any time any infiltrative, destructive or metastatic tendencies indicating a malignant transformation. This evidence thus supports the conception, advanced before, in regard to the Bilharzia tumors, that the mere presence of a parasite in the bladder tissue is not sufficient to endow the epithelial mucosa with malignant properties in spite of its apparent stimulating effect upon the proliferative activity of this tissue.

Brief mention may be made of the frequent occurrence of bladder tumors (carcinomas, sarcomas, carcinosarcomas) among the Formosan yellow cattle (Bos zebu indicus) in certain regions of this island (Wake and Goto). In some herds 50 to 80 per cent of the animals, particularly the females, are affected by this disease, the causation of which is still unknown.

4. MECHANICAL TRAUMA

The question regarding the existence of accidental traumatic relations to the causation of tumors of the urogenic organs is of practical importance only in connection with neoplasms of the kidney. The protected location and the anatomical character of the other parts composing the urogenous system make them apparently less liable to traumatic influences of accidental nature or more readily accessible to diagnostic and therapeutic procedures (urethra), which enable the early determination of the extent and nature of the traumatic effects and their therapeutic mitigation.

The trauma, which is allegedly connected with the development of a renal tumor, consists in an injury to the flanks caused by a fall on this region, a blow against the back by a hard object (board, etc.), a blow with a foot, an excessive strain of this region, while lifting a heavy object, the excessive effort

exerted in vomiting, etc. The anatomical effect of such injuries may be envisaged as hemorrhages into the perirenal or renal tissue with or without direct destruction of renal parenchyma and the subsequent development of local circulatory disturbances in the renal tissue.

The renal tumors with alleged traumatic causative relations are, in general, hypernephromas, according to the information available. It is well to remember that the histologic diagnosis between hypernephroid tumors and certain types of clear-celled renal carcinomas is considered as difficult and that, therefore, in the past many renal carcinomas have been incorrectly recorded in the literature as hypernephromas. The accounts of traumatic renal tumors include for this reason in all probability neoplasms of suprarenal as well as renal histogenesis.

The mention of a trauma preceding the first symptoms of a renal tumor appears relatively rarely in the history of patients with this neoplasm, when a comparison is made with blastomas of other regions, such as the breast. In a series of 177 cases of hypernephroma analyzed by Rückert, trauma was noted in 8 cases, of which Jorns considered only 4 as worthy of any serious consideration in relation to the tumor. A somewhat higher incidence of trauma existed in a series of 43 cases of hypernephroma compiled by Jorns, who found such an incident mentioned in 9 cases, while Kümmel listed among 134 hypernephromas 12 with a preceding trauma. The presence of one single case with a traumatic history of some significance in a series of 101 cases of renal tumors, 82 of which were hypernephromas, was recorded by Deuticke. Walker, cited by Pasteau, reported, on the other hand, 142 renal neoplasms in children with a traumatic history present in 30 cases. Individual cases of this type have been placed on record by Pasteau (1); Stern (2); Pendl (1); and others.

From an analysis of the various reports it becomes apparent that in the great majority of these cases the trauma was coincidental to a pre-existing tumor, inasmuch as symptomatic evidence of a well developed tumor was obtained soon after the accidental injury (Stern; Jorns; and others). The trauma thus simply called the attention to the tumor and thereby had actually a beneficial effect in some instances, because medical aid could be given at an earlier date than ordinarily, as hypernephromas run an insidious course, may remain symptomatically silent for a long time, and may exhibit the first demonstrable neoplastic manifestations through metastases rather than through the primary growth. In other cases the trauma evidently aggravated the course of a pre-existing tumor by hastening the development of generalized metastases resulting from a traumatic injury to the blood vessels, facilitating thereby the neoplastic invasion of the vascular lumina, and the hematogenous metastatization (Jorns).

Thus while the very rapid appearance of neoplastic symptoms, following a trauma to the renal region, indicates the pretraumatic existence of the tumor,

the elapse of several years (7 years in one case of Jorns, 13 years in the case of Pendl) between the trauma and the neoplastic manifestations makes the existence of any causal relation between injury and blastoma highly unlikely. Even the consideration that hypernephromas may show a stationary growth over a number of years is without influence, as reliable evidence in support of such a contention scarcely exists, removing thereby the argument into the sphere of pure conjecture. The cases in which a definite decision is difficult on account of the circumstantial evidence favoring the existence of a causative relation between trauma and renal tumor exhibit the following features:

1. The trauma involved the flank of the body, including the renal region, and thus the site of the tumor.

2. The injury is followed by demonstrable renal disturbances, such as hematuria, pain in kidney region, etc.

3. Symptoms indicating the subsequent development of a renal neoplasm appear, with or without intermediary or bridging symptoms, several months to two years after the accidental injury.

The intervening period is sufficiently long to permit the development of a blastoma of renal or suprarenal origin to attain such a size and extent that definite subjective and objective symptoms may be demonstrable. The existence of causal interrelations may be considered as plausible under these circumstances for medico-legal purposes. Additional support for such a decision may be derived from the following conception advanced by several investigators (Kümmel; Winkler; Seeliger; Rückart; Hartman, and others): Trauma to the kidney region represents an important realization factor of hypernephromas by activating aberrant cellular complexes of the suprarenal cortex, displaced into the renal tissues, into an excessive proliferation assuming a neoplastic character.

While such an argument can draw a certain amount of support from an analogy with the malignant transformation of cutaneous nevi under the influence of a single trauma, there still remains the fact that the large number of small suprarenal cortical cellular complexes, rather regularly found along the course of the ureters and certainly also at times exposed to traumatic influences, scarcely ever have given rise to the development of hypernephromas. Ewing has emphasized in this connection that it is an unproven and hazardous theory that trauma may excite a silent tissue rest or miniature adenoma. Such a stimulus may come, in his opinion, more likely from changes in the functional demand placed upon the suprarenal tissue by the influence of hormonal factors, especially those of the sex glands and the pituitary. It may finally be mentioned that the presence of a hemorrhage or old blood pigment around the tumor found at autopsy cannot be considered as any proof of a traumatic etiology, because hemorrhages are frequently present in and around this type of neoplasm (Knox).

Brief mention may finally be made that Daels and Biltris noted the develop-

ment of malignant neoplasms of the kidney (fusocellular carcinoma and fusiform, giant cellular sarcoma of the kidney) in 2 out of 22 guinea pigs twenty-two months after the implantation of a radium seed into this organ.

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[VI]

OCCUPATIONAL AND ACCIDENTAL HYPERPLASTIC AND NEOPLASTIC DISEASES OF THE BLOOD FORMING ORGANS

1. GENERAL ANATOMICAL CONSIDERATIONS

THE location of the hematopoietic organs in the body, situated beneath the surface lining of the skin, and the respiratory, alimentary, and urogenital tracts, renders these tissues inaccessible to direct contact with any exogenous agent. The hematopoietic tissues are found in the marrow cavities of the bones, in the spleen, lymph nodes, and in the isolated lymph follicles present in the mucous membranes of the respiratory and alimentary canals. Exogenous agents acting upon these tissues must penetrate through the epithelial covering of the organs of primary contact (skin, respiratory, alimentary, and urogenital system), and enter the tissue juices, blood, and lymph fluid, before they can exert any effect upon the various cellular elements composing the hematopoietic tissues.

The different types of reactions, which may be elicited in these organs under the influence of exogenous agents, reflect the complex cellular and functional nature of the various parts composing these tissues. A brief summary of the different cellular types and their respective local distribution in the hematopoietic organs may be helpful toward understanding the nature and significance of the blood dyscrasias to be considered in relation to occupational exposures.

The bone marrow is composed normally of reticular cells, myeloblasts, megakaryoblasts, erythroblasts, and their developmental derivatives. The corpuscular elements released form this tissue into the circulating blood are the polymorphonuclear leucocytes, mononuclear leucocytes, erythrocytes, and platelets. The lymphoid organs consist of reticular and reticulo-endothelial cells along with lymphoblasts and their developmental derivatives, which supply the circulating blood with lymphocytes and mononuclear leucocytes.

For the purpose of this presentation it is not essential to discuss in detail the various attributes of the different conceptions held in regard to the existence of a stem cell common to all cells of the hematopoietic tissue (hemocytoblast), or of the several separate stem cells distinguished for the different types of pigment-bearing and nonpigment-bearing cells. Some authors believe in the possibility of morphological and functional transitions

from one cell form into another (lymphocytes may be transformed under certain conditions into polymorphonuclear leucocytes, or mononuclear leucocytes may become lymphocytes, etc). The mere mention of these controversies may suffice to emphasize the uncertainties which still exist concerning some of the fundamental aspects of hematic phenomena, which have a direct and important bearing upon the proliferative manifestations produced or precipitated by the action of certain occupational agents.

The following presentation of the occupational hyperplastic and neoplastic disease conditions of the hematopoietic tissue adheres to the scheme usually followed for the classification of blood diseases. There are two main groups: first, diseases affecting the erythropoietic tissue and the hemoglobin-carrying, nonnucleated erythrocytes; and second, the diseases of the leukopoietic tissues and the nonpigmented, nucleated leucocytes.

2. OCCUPATIONAL ERYTHROCYTOSES

A. General Characteristics and Classifications of Erythrocytoses

A pathological increase in the number of erythrocytes represents a symptomatic manifestation of numerous occupational and nonoccupational diseases. These increases differ widely among one another in both their etiology and causative mechanisms (Otto; and Massione). The inclusion of a chapter on the erythrocytotic changes of occupational derivation is justified, since many of these conditions are definitely of a hyperplastic nature. Furthermore, they resemble in their symptomatology corresponding disorders of nonoccupational origin and show, sometimes, a great similarity to the cryptogenic polycythemia of the Vaquez-Osler type and the hypertonic variety of the Gaisboeck type. Various investigators have even advanced claims that some of these occupational erythrocytoses may be the precursors of the blastoma-like polycythemias into which they may be ultimately transformed, provided the causative factors are intensive enough and are permitted to act over a sufficient period of time.

For the proper identification and evaluation of these erythrocytotic conditions they must be compared with the erythrocytic status present in the circulating blood of healthy individuals. The number of erythrocytes for the normal male is considered usually to be in the neighborhood of 5.0 million and for the normal female approximately 4.5 million. Otto stated that erythrocytotic reactions begin in men with values of more than 4.8 million erythrocytes and in women with values of 4.6 million erythrocytes. The classification of erythrocytotic manifestations by this author is based on the degree of the numerical increase of the red blood cells and is as follows: erythrocytoses are characterized by erythrocytic values ranging from 5.0 to 5.5 million; hyperglobulisms are characterized by erythrocytic values of 5.6 to 6.5 million; while polyglobulisms are characterized by erythrocytic counts in excess of 6.5 millions. This classification is unsatisfactory from various viewpoints.

The use of terms, which as a rule are employed as synonyms, for the designation of arbitrary groups possessing no definite clinical or scientific significance is superfluous and confusing. Numerical differences are much less important in the characterization and differentiation of erythrocytic increases than their variations in etiology and causative mechanism. The main objection against the adoption of this classification for distinguishing between the different occupational erythrocytoses is that the first group of erythrocytotic reactions is definitely placed within the normal erythrocytic range, and the second group may possibly fall within the same normal range.

The probability of the first two groups of Otto's classification falling within the erythrocytic range observed for normal individuals is enhanced by considering the findings of several investigators, as to the number of erythrocytes found in such individuals. In normal healthy men (20 to 30 years) Bierring (Sweden) found in four cases a mean of 5.05 million; Bie and Möller (Denmark) reported for ten cases a mean of 5.53 million; Gram and Norgaard (Denmark), for seven cases a mean of 5.39 million; Horneffer (Germany) for forty cases, a mean of 4.96 million; Haden (Missouri) for twenty cases, a mean of 5.08 million; Osgood (Oregon) for 137 cases, a mean of 5.39 million; and Wintrobe and Miller, and Wintrobe and Landsberg in 186 cases, from different parts of United States, reported a mean of 5.40 million. According to Wintrobe, the corresponding figures for women (of the same age group, 20 to 30 years) based upon fifty individuals are somewhat lower than those for men, having a mean of 4.78 million and ranging from 4.64 to 5.22 million. The importance of these studies becomes even more marked, in the light of Otto's classification, if the range of erythrocytic values found in the above-mentioned male series is considered. Osgood reported that the normal values ranged from 4.70 to 6.10 million (7.3 per cent of the cases being above 6.00), while Wintrobe recorded the limits of normal as being between 4.60 and 6.20 million (60 per cent of his second series of 86 cases being above 6.00, two cases having 7.35 and 7.53 million, respectively). None of the individuals with high erythrocytic figures showed any (clinical) evidence of polycythemia; while those with the lower figures were all underweight and not quite normal physically.

Wintrobe reported that the number of erythrocytes, the concentration of hemoglobin, and the relative cell volume is correlated with the body weight in males and with the surface area in females. Pearl and Miner, by biometric analysis, found that the cell volume seems to be related somewhat to the stature of the male. Leichtenstern claimed that in general lean, muscular men have more erythrocytes than obese individuals, and a similar opinion was held by Engel. Apart from these constitutional factors there are numerous, nonoccupational disease conditions which may bring about an increase in the number of erythrocytes (Otto). Considering the figures given as normal by the above-mentioned authors, and taking cognizance of the large number

of disorders listed by Otto as causes of symptomatic erythrocytoses, values above 5.50 million red cells are relatively uncommon among the large number of persons, in many instances not seriously ill and without organic disorders, routinely examined in hospital laboratories. In this light the high normal figures given by Wintrobe can scarcely be considered significant. Erythrocyte counts above six million, and especially those well above seven million cannot be regarded, under any circumstances, as representing erythropoietic reactions of normal individuals, even in the absence of any manifest organic lesions. Such exceptionally high erythrocytic values must be considered as constitutional abnormalities of possibly familial nature (Nadler and Cohn). From the numerous hematalogic studies on persons industrially employed of various age groups and occupations, the average member of this class rarely shows erythrocytic values of the magnitude described by Wintrobe, and Osgood. The acceptance of the figures given by these authors, as a representative standard and for comparison in occupational erythrocytotic disorders, appears to be unjustified. Erythrocytic values ranging from 5.50 to 6.00 million and hemoglobin concentrations above 18.0 gm are suggestive, and erythrocyte counts above 6.0 million are indicative of abnormal erythropoietic activity (Humperdinck), when observed in individuals exposed to certain occupational hazards, unless preoccupational data are available which prove the non-occupational origin of these manifestations.

While the numerical classification of the symptomatic erythrocytoses is of little help, the classification of these conditions on the basis of their causative mechanisms is of distinct value. It is not only essential for an intelligent understanding of, and the distinction between, the different factors which may produce an apparent increase in the number of erythrocytes, but it is also of special significance for the correct medico-legal evaluation of these conditions when resulting from occupational contacts. The following classification, patterned after one recently proposed by Harrop and Wintrobe, divides the symptomatic erythrocytoses into two main types, the spurious one and the actual; each of which have several subvarieties.

Spurious Erythrocytoses

Spurious erythrocytoses are conditions in which the total number of erythrocytes present in the blood is not appreciably altered. The apparent increase is caused by (1) a disturbance in the normal ratio between the liquid and cellular elements of the blood (relative erythrocytoses) or (2) results from general or local changes in the distribution of the erythrocytes (distributory erythrocytoses).

Relative erythrocytoses ensue when the plasmatic fraction of the blood is decreased markedly by escape into the tissues (as in shock after excessive burns and removal of large amounts of ascitic fluid), or following insufficient water replacement, excessive loss of water through the bowels [cholera and

toxic colitis (mercury, arsenic, and ricin)] (Möschl), or by prolonged vomiting (hyperemesis gravidarum and pyloric stenosis), usually accompanied by decreased resorption of fluid.

Distributory erythrocytoses may be of two types, general or local. In the generalized type they are the result of transitory shifts of greater numbers of erythrocytes from the splenic storehouse of these cells. This distributory erythrocytosis, following splenic contraction, occurs after excessive physical exertion with dyspnea. The general type may be observed in athletes and has been experimentally produced by physical exercise in dogs (Davis and Brewer). It may occur as a result of blood acidosis (Detre and Zárday), or after an injection of adrenalin (von Haam).

The local, congestive, distributory type of erythrocytosis is observed after thrombosis of the portal vein, or following compression of the superior vena cava by a mediastinal tumor, which causes a polyglobulosis in the vessels of the upper part of the body.

Actual Erythrocytoses.

Actual erythrocytoses are characterized by an absolute increase in the number of erythrocytes in the circulating blood, due to an overproduction of red cells by the erythropoietic tissue stimulated to increased activity. This overproduction of erythrocytes may be brought about by a known or unknown agent of endogenous (intrinsic gastric factor?) or exogenous (physical or chemical) origin. It may result from an accumulation of erythrocytes in the blood following an abnormally slowed rate of physiologic, erythrocytic destruction (transitory polyglobulia after extirpation of the spleen?). This type of erythrocytosis or erythremia is usually accompanied by a simultaneous increase in the concentration of hemoglobin and the total volume of blood (plethora).

In the following presentation of the different, occupational, symptomatic erythrocytoses, arranged according to their etiology, more than one causative mechanism, in several of these pathological manifestations, may be active simultaneously or successively in their production.

a. Chemical Agents

I. Erythrocytosis following exposure to high altitudes

(Reduced oxygen tension)

The first observation in regard to the effect of high altitude, with its thinned air and lowered atmospheric pressure, upon the number and hemoglobin content of the erythocytes was made by Viault in 1890. This investigator studied the inhabitants of the Peruvian Andes and observed an increase in these hematic constituents. This discovery has been confirmed subsequently by numerous investigators in various countries who have studied this phenomenon thoroughly (Barcroft; Talbott; Laquer; Zuntz, Loewy, Müller and

Caspari; and Loewy). The practical significance of this hemantic alteration, as viewed from an occupational standpoint, was restricted, until rather recent years, to permanent or transient inhabitants of regions of high altitudes (mountaineers, miners, and herdsmen) or an occasional balloonist. The rapid development which civil and military aviation has made lately exposes a constantly increasing number of individuals to the effects of high altitudes, and increases the general importance of this blood reaction (Koelsch and Lederer).

The symptomatic erythrocytosis observed as an effect of high altitudes may be divided according to the causative mechanisms into two types or phases. The sudden and rapid ascent to high altitudes, such as experienced by the personnel of airplanes and balloons, as well as mountain climbers, is followed during the first day by an increase in erythrocytes, which may be as much as twenty-six per cent of the original number (Kündig; Morawitz and Denecke; and Barcroft). The erythrocytosis thus observed is of the spurious type, since it is produced by distributory shifts of the blood cells into the peripheral vessels from the contracted spleen. The initial rapid increase is followed on subsequent days, provided the sojourn at high altitudes is prolonged, by a further rise in the number of erythrocytes. The peak of this process is attained when acclimatization has occurred, that is within one to three weeks (Culpepper; Meyer and Seyderhelm; and Barcroft).

The erythrocytosis of the second phase is characterized by an actual increase in the number of red cells, the concentration of hemoglobin, and the total blood volume (Zuntz; Liebesny; Laquer; and Henderson). There is an increase simultaneously in the oxygen capacity of the blood which, according to Talbott, averages 28 per cent at an elevation of 5,340 meters. While appreciable individual variations exist in the responsiveness of the erythropoietic tissue to changes in altitude, the magnitude of hematic alterations approximately parallels changes in the altitude. Bürker found that at an elevation of 2,000 meters the increase in erythrocytes varied (in different individuals) between four and twelve per cent, and that hemoglobin concentration increased between eight and eleven per cent. Schröder observed erythrocytic counts of 5.80 million at an altitude of 561 meters; Wolff reported counts of 5.97 million at an altitude of 700 meters; Kundig observed red cell counts of 6.55 million at 1,560 meters; Egger found 7.00 million cells at 1,800 meters; Viault reported 8.0 million erythrocytes in the Peruvians living at an altitude of 4,000 meters; and Laquer claimed that true polyglobulia begins with an altitude of 1,500 to 1,600 meters. There seems to be an upper limit to this erythrocytic increase with rising elevations, as Talbott reported that there was no difference in the oxygen capacity of the blood in individuals living at an altitude of 5,340 m and 6,140 m, respectively.

Since the erythrocytes and hemoglobin increase in about the same proportion, there is no change in the color index, according to Schneider and Havens.

This observation is in disagreement with the finding of Hurtado who, in a study of a small number of Peruvian Indians, observed that they possessed erythrocytes larger than normal but incompletely filled with hemoglobin. The increase in viscosity resulting from the greater density of the erythrocytes is, to a certain extent, neutralized by a drop in the concentration of the highly viscous proteins and globulins in the plasma (Frenkel-Tissot).

Several important and convincing observations support the conception that the secondary erythrocytic phase is the result of an abnormally stimulated, erythropoietic activity of the bone marrow. The number of reticulocytes in the circulating blood of man is definitely and appreciably increased (Barcroft; and Hurtado), and nucleated red cells appear in the blood of animals (Schauman and Rosenquist). Plethora, or an increase in total blood volume, exists in man (Henderson; and Laquer), as well as in animals (Jaquet). The erythropoietic activity of the bone marrow is stimulated, according to Otto and Zadek, and the regeneration of the blood at an altitude of 3,000 meters proceeds at twice the speed as that observed at sea elevel (Heimann). This points to an activated regeneration, and possibly to an actual hyperplasia of the marrow at high altitudes. The iron content of the liver is decreased during residence at high elevations, which is indicative of an increased ultilization of this substance in erythropoiesis (Zuntz; and Miescher). The amount of erythroblastic bone marrow is increased, according to the observations of Zuntz made on dogs kept at an altitude of 2,000 meters.

The lowered oxygen pressure present at high altitudes represents the causative mechanism eliciting the described erythropoietic response. The insufficient oxygenation of the blood existing under such conditions (anoxemia) exerts a stimulating effect upon the erythropoietic activity of the bone marrow, resulting in a compensatory increase in the number of erythrocytes and the concentration of hemoglobin. From the oxygen dissociation curve of the blood, a defective saturation with oxygen occurs at an oxygen tension of 70 mm. (normal tension 100-110 mm.) in the alveolar air. Such interrelations between reduced oxygen tension and defective saturation exist in an individual at muscular rest at an altitude of 2,000 meters. The effects of a lowered oxygen pressure are experienced by many persons at a much lower altitude due to decreased CO_2 tension present under such conditions (800 meter altitude). Physical exertion may change the oxygen requirements, evidenced by the presence of a decreased CO_2 combining power. This, according to Staehelin, is of a compensatory nature; while Detre believes the acidosis is the cause of the erythrocytosis observed. The contention of Detre is supported by the experimental production of an erythrocytosis induced by an acidosis, and in turn removed by the subsequent inhalation of oxygen or the intravenous administration of alkalis.

The course and persistence of the erythrocytotic condition depends upon the duration of the sojourn at high altitudes. As it is a compensatory reaction

it becomes permanent for the inhabitants of regions, such as the Peruvian Andes, and causes in these individuals a widening of the vascular lumina (for circulatory reasons). The return to the lower altitudes is followed by a rapid reduction in the number of erythrocytes during the first days, and then a gradually slower one until normal values are reached again. The decrease in erythrocytes is not accompanied by the appearance of any degenerated forms (Morawitz and Denecke).

This conception of the ready and complete reversibility of the erythrocytosis of high altitudes is not shared by Monge, who maintained that a chronic type of erythrocytosis occurs, which may manifest itself even after acclimatization has apparently developed. According to Monge, this chronic type may become permanent and form an etiological link to polycythemia vera (Vaquez). Morawitz and Denecke pointed out that this assertion so far lacks adequate clinical proof, an opinion with which Harrop and Wintrobe agreed. The latter two authors mentioned that the cases reported by Monge did not show, in most instances, the abnormal leucocytic forms, the leucocytosis, and the large number of immature erythrocytes that are characteristic for the hematic changes of the Vaquez disease. Talbott has stressed the absence of the morphologic changes in the blood in erythrocytoses caused by lowered oxygen pressure, such as observed in polycythemia vera.

II. ERYTHROCYTOSIS CAUSED BY CARBON MONOXIDE POISONING

The erythrocytosis associated in some instances with carbon monoxide poisoning shows many similarities with that induced by exposure to decreased oxygen partial pressure occurring at high altitudes (Engel). This blood reaction has considerable practical importance since carbon monoxide poisoning shares with lead poisoning the foremost position among industrial poisonings.

Individuals employed in the following occupations are exposed to acute or chronic carbon monoxide poisoning: workers in gas plants and gas generating factories, blast furnaces, smelting plants, nickel refineries (operated by Mond process), glass plants, and workers sealing cellophane wrappers with heat. Other individuals so exposed are stokers, chauffeurs, garage workers, attendants of gasoline engines (motor boats, and small war craft), gunners in gun turrets and machine gun pits, pilots of airplanes, firemen, and traffic policemen.

The investigations of Farmer and Crittenden on steel mill workers have shown that saturation or equilibrium of the blood with the prevailing concentration of carbon monoxide, found in the environmental mill atmosphere, is accomplished in one to three hours. After this period the concentration of carbon monoxide in the blood tends to remain constant. The carbon monoxide is present in the blood of these workers for a period of sixteen hours or more after exposure has ceased. It gradually decreases during this interval from a level averaging 6.26 per cent saturation (at the end of the working shift)

to one ranging from 0.3 to 5.0 per cent. At the beginning of the new shift, on the following day, the average concentration of blood carbon monoxide is 2.11 per cent, the residual carbon monoxide varying considerably with the individual. This variability may account for the varying severity in the symptomatology, and especially in the type of blood reaction observed in individuals subjected to carbon monoxide under apparently equal conditions of exposure.

Beck maintained that air concentrations of carbon monoxide as low as 0.05 per cent inhaled over prolonged periods may become dangerous and be responsible for an erythrocytosis. Sayers and his co-workers found that men exposed from four to seven hours daily, for a period of 68 days, to mixtures containing 2 to 4 parts of CO per 10,000 parts air, showed a distinct increase in erythrocytes and hemoglobin.

Erythrocytotic blood reactions resulting from exposures to carbon monoxide of an occupational origin are common. They have been reported by Koelsch and Lederer; Zadek; Beck; Voit and Schmidt; Sayers, Yant, Levy and Fulton; Martland; Litzner; Egdahl; Humperdinck; v. Jaksch; Reinhold; Naegeli; v.Limbeck; Silbermann; Salkind; Münzer and Palma; Karasek; and Jenkins. Among the cases of carbon monoxide erythrocytosis reported, there are an appreciable number which possessed erythrocytic values well within the normal range or located within the suspicious range extending from 5.5 to 6.0 million. Davies studied the blood of 175 individuals employed at blast furnaces (steel mills), and observed that 64 per cent of these men had erythrocyte counts over 5.0 million, but only 2.2 per cent exhibited counts over 6.0 million. These findings are very similar to those recorded by Osgood for his normal group. Symanski from his examination of a gas plant personnel found that only 26 per cent showed a slight increase in erythrocytes, present mainly in muscular, well-developed individuals of the pyknic type, which remained well within the suspicious range. There exists sufficient, satisfactory clinical and experimental evidence attesting the erythrocytotic effect produced by exposure to carbon monoxide gas. Ziegler reported the presence of 12 cases of erythrocytosis in a series of 36 cases of chronic poisoning with carbon monoxide (32 per cent). An increased number of erythrocytes and amount of hemoglobin was observed by him in 37 out of 146 workers of gas plants, who had no symptoms of poisoning. The erythrocyte counts in some of these cases ranged from 6.0 to 7.5 million, and the erythrocytotic reaction persisted in several cases for several years being accompanied by a swelling of the spleen. In other cases belonging to this group the number of erythrocytes diminished rapidly after the cessation of exposure to carbon monoxide. An additional case of polycythemia, after repeated carbon monoxide poisoning, was recorded recently by Dittmar. This investigator noted the presence of an erythrocytosis of 6.91 million red cells and 125 per cent hemoglobin in a fireman, 46 years old, who had suffered repeatedly during his work from

carbon monoxide poisoning, and who had developed the neurological symptoms of a degeneration in the region of the corpus striatum. As this individual showed 6 months after cessation of his work a definitely increased number of erythrocytes, a leucocytosis, a lymphopenia, an enlarged spleen, a thrombocytosis, and in increased metabolism, Dittmar considered the case a genuine polycythemia following chronic carbon monoxide poisoning. Apfelbach and Karasek, from observations in 665 steel plant workers, found erythrocytic increases from 6.00 to 9.67 million. Litzner and Beck reported erythrocytic values definitely located in the erythrocytotic range. The hemoglobin concentration varied between 95 to 125 per cent depending upon the number of erythrocytes. Immature erythrocytes may be present in moderate number. The leucocytes are present in normal numbers or are increased (maximum 13,000), showing a shift toward the mononuclear elements. Myelocytosis and eosinophilia, indicative of the existence of an irritated bone marrow, are observed occasionally.

The experimental production of a carbon monoxide erythrocytosis was accomplished successfully by Nasmith and Graham. Guinea pigs, exposed for several weeks to an atmosphere containing CO (producing a 25 per cent saturation of the hemoglobin), exhibited an increase in erythrocytes from 6.0 to 8.0 million and in hemoglobin from 88 per cent to 115 per cent. When the saturation of carbon monoxide was raised to 35 per cent, the erythrocytes rose to 9.5 million. In one animal kept for one year at a 25 per cent saturation, for an additional three weeks at 35 per cent, and for a second three weeks at 45 per cent saturation, there were 10.7 million erythrocytes and 109 per cent hemoglobin one month after the cessation of exposure. When this animal was exposed subsequently to normal atmospheric conditions for one month, the number of erythrocytes and the concentration of hemoglobin returned to their normal values. It was noticed that degenerated erythrocytes appeared in the blood during the first twenty-four hours of exposure to an atmosphere containing carbon monoxide. This change was followed by the appearance of erythroblasts after sixty to seventy hours of exposure. Both cellular phenomena receded after the first week of exposure, but reoccurred following every increase in the carbon monoxide concentration. Similar results were obtained by Voit and Schmidt in guinea pigs exposed to inhalations of air and CO, which developed erythrocytosis, leucocytosis, and hyperglycemia, following acute and chronic carbon monoxide poisoning. Erythrocytotic reactions following carbon monoxide poisoning were observed by Williams and Smith in rats, by Gerbis in dogs, and by Salkind in guinea pigs. The erythrocytosis produced by exposure to CO in rabbits varied, according to Ziegler, in its tendency to persist after the arrest of treatment from that obtained in other animals and resembled in this respect those seen by him in man.

An erythrocytosis may appear after an acute attack of carbon monoxide

poisoning and after repeated exposures to this gas at lower concentrations. Pfeil even asserted that it is observed only after acute CO poisoning; but Beck has pointed out and proved that it is a reaction observed rather frequently with chronic exposures to low concentrations of the gas. The affected individual has symptoms (pallor, sore tongue, neuralgia, headache, vertigo, tremor, weakness, slow pulse, and low basal matabolism) usually associated with a severely anemic appearance, but examination of the blood demonstrates the presence of an erythrocytosis. However, only a certain percentage of exposed individuals react with erythrocytotic manifestations, while the others develop an anemia of a more or less severe degree (Litzner; and Beck).

Inhalation of carbon monoxide results in the formation of a pathologic and rather stable abnormal type of hemoglobinous compound, carbon monoxide methemoglobin. This substance is incapable of carrying oxygen, and its production causes an impairment of the proper oxygenation of the blood (anoxemia). In an acute attack of carbon monoxide poisoning, the organism attempts to overcome this handicap by the contraction of the spleen, throwing a reserve quantity of erythrocytes into the circulation, which improves the internal respiration (Litzner). This auxiliary mechanism is insufficient with prolonged exposure, and then an increased production of erythrocytes caused by a stimulation of the bone marrow occurs. This is indicated by the appearance of erythroblasts in animals and of myeloid elements and leucocytosis in man. Pfeil maintained that the stimulus eliciting the erythrocytotic response originates from lesions produced in the brain by the action of carbon monoxide. Recent investigations of Kohn-Abrest suggest that a difference may exist in the fixation of carbon monoxide in the tissues following acute and chronic poisoning. He observed that CO absorbed in small amounts over prolonged periods is retained in the body for a much longer time than when it enters the body in larger amounts during an attack of acute poisoning, after which it is eliminated within a few hours after cessation of the exposure. Dittmar pointed out that the concentration of carbon monoxide responsible for chronic poisoning was usually too low to cause any significant impairment of the oxygen carrying power of the blood, thus causing an anoxemic condition. This investigator was inclined to dismiss any acidotic mechanism as the cause of the erythrocytosis in this condition, because the blood possesses under these circumstances an alkaline reaction. In view of the cerebral lesions commonly found with this type of poisoning, and considering that polycythemia has been produced experimentally in animals by setting injuries to the midbrain (Castex; and Schulhof and Matthies), Dittmar believed that the degenerative changes in the brain are etiologically related and essential for the development of an erythrocytosis in carbon monoxide poisoning.

The symptomatic erythrocytosis caused by exposure to carbon monoxide and producing an acute or chronic type of poisoning is of a transitory nature; but, in contrast to the anoxemic erythrocytosis seen at high altitudes, the carbon

monoxide reaction in some instances may persist for some months or even years after cessation of exposure (Koelsch and Lederer; Humperdinck; Ziegler; and Dittmar). No reliable and conclusive evidence seems to be available, as to whether such protracted erythrocytotic reactions may be transformed ultimately into a typical polycythemia vera. v. Jaksch reported a case of polycythemia vera which followed an episode of carbon monoxide poisoning, and Litzner made a similar observation. The latter author stated that etiological interrelations between carbon monoxide poisoning and polycythemia should be acknowledged, whenever symptoms of blood dyscrasia follow soon after an attack of carbon monoxide poisoning.

III. ERYTHROCYTOSIS FOLLOWING EXPOSURE TO HYDROGEN SULFIDE, NITROSE GASES, AND HYDROGEN CYANIDE

The erythrocytoses observed after inhalation of air possessing a lowered oxygen tension or containing an admixture of carbon monoxide exemplify the general principle that interference with the proper oxygenation of the blood may result in the development of compensatory, hyperplastic, erythropoietic reactions. Additional evidence is provided by the occurence of erythrocytotic manifestations after the exposure to certain noxious gases, which cause the production of sulfhemoglobin, methemoglobin, or cyanide-methemoglobin (Otto; Koelsch and Lederer; and Engel).

The presence of polyglobulia and the increase of hemoglobin in workers of a rayon plant was reported by Rodenacker, who attributed these changes to the inhalation of hydrogen sulfide. This investigator found that the erythrocytes, in some instances, were increased to 7.0 million cells, but otherwise the blood was normal and the individuals did not exhibit any clinical symptoms of poisoning. Workers employed in cokeries, gas plants, metallurgical establishments, aniline dye manufacture, carbon disulfide production, and soda manufacture by the Leblanc process are exposed extensively to this hazard.

The occurrence of erythrocytosis following the exposure to nitrose gases (NO and NO_2) has been mentioned by Otto. These gases have an irritating action on the respiratory tissues because of the formation of nitrates, and a more general effect upon the blood and circulation resulting from their transformation into nitrites. These general effects are due essentially to methemoglobin formation, the slowing of the circulation with capillary stasis, and the thickening of the blood by excessive perspiration. It is the nitrite effect which must be incriminated for the development of the erythrocytotic manifestations. Occupational contact with these gases exists in all processes which lead to the production of nitric acid or in which this acid or nitrates or nitrites are used (production of nitrobenzol, nitroglycerin, nitrocellulose, picric acid, and the brass industry).

Recent experimental investigations of Hueper and Landsberg on rats have shown that a prolonged exposure to organic nitrites, such as used in the production of explosives, may result in the production of a considerable increase

of red blood cells in response to the hypoxemia, caused by an excessively slowed blood flow and possible methemoglobin formation.

A third group of substances which may cause occupational poisonings of anoxemic character are the cyanides, especially hydrogen cyanide. Hasselmann, who examined the blood of 100 cyanide workers, found relatively high erythrocytic values; erythrocytes ranging from 5.0 to 5.8 million and hemoglobin from 85 to 100 per cent. There were in some instances, a lymphocytosis, basophilia, and eosinophilia. The occurrence of polyglobulia incident to chronic cyanide poisoning was mentioned by Petri. The causative mechanism present appears to be of a complex nature. The erythrocytotic reaction may result from the anoxemia produced by the lowering of the blood pressure, passive congestion, and erythrocytic destruction in combination with the erythropoiesis stimulating effect exerted by small hemorrhages. It is improbable that the erythrocytotic reactions, observed by Hasselmann, were caused by an impairment of the oxygen carrying power of the blood, resulting from the formation of cyanide-methemoglobin.

While it seems certain that such a compound can be formed in the blood in cases of cyanide poisoning, it is generally assumed that this substance is the product of a postmortem phenomenon (Kobert; and v. Zeynek). Cyanide-methemoglobin is readily formed in vivo in the presence of methemoglobin. The suffocating action exerted by cyanides is caused by an inhibitory effect upon the oxidases of the cells, and renders them unable to utilize the oxygen carried by the blood (histiotoxic anoxemia). At the present time the evidence supporting an erythrocytotic reaction in cyanide poisoning is not quite reliable and definite. Further investigations are indicated, since the hazard of a repeated exposure to cyanides exists for a considerable number of industrial workers, especially those employed in gas works, at coke ovens, blast furnaces, in dyestuff factories, gilding works, gold mines, airplane manufacture, and with fumigation of ships, buildings, and orchards.

IV. ERYTHROCYTOSIS FOLLOWING EXPOSURE TO AROMATIC HYDROCARBONS AND THEIR NITRO- AND AMINO-DERIVATIVES

Benzol and its homologues, xylol and toluol, and their nitro- and amino-derivatives have been incriminated as responsible for the production of erythrocytotic reactions in workers exposed to them (Zadek; and Hamilton). These compounds exert a destructive action upon the erythrocytes and the erythropoietic tissue (benzol), and are responsible for methemoglobin formation (nitrobenzol and aniline) or may produce both effects (phenylhydrazine, pyrodin, and toluylene diamine). These are usually associated with degenerative lesions in the liver. In the presence of an increased production of hydrogen sulfide in the intestine these compounds favor the development of sulfomethemoglobin, which is more stable than the simple methemoglobin and may persist, in traces, over intervals of weeks and months (Snapper; and Harrop and Waterfield). As the effect of both types of pathologic blood pig-

ments upon the oxygen metabolism is identical with that exerted by carbon monoxide methemoglobin (the production of an anoxemia), occupational exposure to these aromatic compounds may be followed, in some instances, by a transitory erythrocytotic reaction (Naegeli; and Seyderhelm). Actual destruction of erythrocytes and degenerative changes in the liver may assist in eliciting this response, by stimulating the regenerative activity of the bone marrow.

The occurrence of an initial erythrocytotic phase with a corresponding increase of hemoglobin in female workers suffering from benzol poisoning, was reported by Koelsch and Lederer; Hamilton-Paterson; and Gall. Smith and Hunter observed the occurrence of massive metaplastic erythropoiesis in the spleen, and to a lesser degree in the liver, in a case of benzene poisoning succumbing to aplastic anemia, leukopenia, and thrombocytopenia. This atypical and excessive regenerative activity of a heterotopic, potentially hematopoietic tissue represents an attempt to compensate for an inadequate regeneration of the bone marrow. Langlois and Desbouis confirmed the erythrocytotic observation of Koelsch and Lederer in dogs, rabbits, guinea pigs, and pigeons exposed to prolonged inhalation of benzol and mononaphtha. Gerbis recorded a similar reaction after exposure to nitrochlorobenzol. A definite rise in the number of reticulocytes, which persisted for the duration of the experiment, was noted in animals exposed for a period of three months to benzol fumes by Paul, Friedlander and McCord. They concluded that exposure to benzol fumes in low concentration has a stimulating effect on the blood forming organs, especially the erythroblastic tissues. Genkin and Raschewskaja concluded from their study of aniline workers that there existed a decreased respiratory activity of the blood by the formation of methemoglobin which resulted in polyglobulia and an increase of the hemoglobin concentration.

Observations made by Gaeta in rabbits poisoned with parenterally administered aniline support the possible occurrence of such erythremic reactions, because he found, in the presence of a severe anemia with numerous immature erythrocytes in the blood, an intensive erythropoietic reaction of the bone marrow, and a hyperplasia of the leukopoietic and megakaryopoietic elements. Experimental poisoning with aniline, benzol, nitrobenzol, phenylhydrazine, pyrodin, toluylene diamine, pyrogallol, and saponin yielded erythrocytotic responses in the hands of several investigators. In rabbits treated with small doses of phenylhydrazine, Schustroff as well as Wyssotsky obtained an erythrocytotic response characterized by the appearance of immature erythrocytes in the blood and stimulation of the bone marrow. Similar effects were seen by them following the administration of pyrodin. Using the same compound, Battistini and Rovere observed a transient erythrocytotic phase followed by anemia.

Arrak recorded the development of a persistent polyglobulia, after prolonged administration of small amounts of pyrodin in rabbits (0.0001-0.0002 gm. per kilo of body weight, increasing the dose weekly by 0.1 mgm. because of the gradually increasing tolerance) given for more than 100 days. The number of erythrocytes increased by 13.8 to 37.0 per cent (average 22.0 per cent), and the hemoglobin concentration rose 9.3 to 27.0 per cent (average 19.7 per cent), the hemoglobin response lagging behind the cellular response. Similar erythrocytotic reactions were elicited after the introduction of toluylene diamine in studies conducted by Arrak; Syllaba; and Hertz and Erlich. A persistent type of erythrocytosis in rabbits lasting 77 to 139 days, after repeated administration of 0.01 gm. per kilo of body weight, was again reported by Arrak. There was, in addition to a numerical increase of erythrocytes, polychromasia and elevated cell volume; while the individual cellular size was decreased. The reaction of the bone marrow consisted in a mild increase of immature erythrocytic and myeloid cells. A leucocytosis of a minor degree existed in the rabbits treated with pyrodin. The erythrocytotic reactions produced by pyrodin as well as toluylene diamine receded within 3 to 4 days after cessation of medication.

V. ERYTHROCYTOSIS FOLLOWING OCCUPATIONAL DISEASES OF THE LUNGS

The etiological interrelation between chronic dyspneic conditions, caused by nonoccupational disorders of the respiratory function (pulmonary fibrosis) or of the pulmonary circulation (congenital pulmonary stenosis; acquired, decompensated valvular lesions of the heart; and arteriolar pulmonary sclerosis of unknown origin), and erythrocytotic reactions is well-established. They originate from a stimulus elicited by the congestion of the bone marrow combined with anoxemia of the erythropoietic tissue associated with these pulmonary disturbances. Schuetz claimed that arteriolo-pulmonary sclerosis (thromboarteriitis pulmonalis) is a frequent etiological condition in polycythemia vera. Recent observations by Rosenthal indicate that such circulatory disturbances in the lung may have an occupational basis. From an analysis of ten cases of obliterative pulmonary arteriolar sclerosis, he concluded that an occupational inhalation of iron dust and fumes from benzine, naptha, and similar substances was the cause of the vascular lesions. These lesions consisted of the reduction of the width or the complete obliteration of the lumina of the pulmonary arterioles by atheromatous intimal thickenings and of fibrosis of the media of the larger branches of the pulmonary artery. They caused thereby an impairment of the blood circulation in the lung. The increase in erythrocytes reached 6.69 million, associated in some instances with a leucocytosis (up to 11,500). Stewart and Faulds observed in the lungs of hematite miners having a red pulmonary siderosis an extensive fibrosis of the lung connected with pulmonary arteriolosclerosis.

A second example of symptomatic erythrocytosis following an occupational exposure to fumes possessing an irritative effect upon the respiratory organs, especially the lung, was reported by Rostoski and Crecelius. These authors studied twenty-one workers of a cellulose factory who had been involved in an accident several months previously, during which they inhaled sulfur dioxide (SO_2) and sulfite fumes in high concentration from eight to forty-five minutes. While every one of these individuals exhibited increased erythrocytotic values, these were especially high in several male workers with severe chronic pulmonary changes resulting from the accident (bronchiectases, emphysema, chronic bronchitis, and pneumonia). The highest erythrocyte count recorded was 8.60 million, and the greatest concentration of hemoglobin observed was 133 per cent. The erythrocytotic condition persisted in these workers for several years after the accident, while a red bone marrow was observed in one of these individuals who later died and came to autopsy. The presence of clubbed fingers in two cases was evidence of the severe interference with the pulmonary circulation resulting from the chronic fibrosing alterations existing in the lungs.

While the erythrocytosis observed in this group of cellulose workers was caused, in part, by pulmonary complications following accidental exposure to SO_2 fumes, Seitz pointed out that this explanation could not be applied to erythrocytotic increases and hemoglobin elevations observed by him in a group of cellulose workers, which were symptomatically normal and exhibited an unusually healthy complexion. Nine of the twenty-eight workers examined had hemoglobin values above 105 per cent (corrected Sahli), and the highest concentration was 123 per cent. He pointed out that these workers were exposed to the inhalation of SO_2 fumes during their routine work. Since large scale production of cellulose for various industrial purposes is rapidly increasing in all civilized countries and employs thousands of workers, it seems to be of great importance that adequate attention be paid to the occurrence and incidence of this symptomatic blood dyscrasia among workers in this industry. The erythrocytotic action following inhalations of sulfur dioxide was confirmed by Ronzani by experimental studies in animals.

The pneumoconiotic fibrosis of the lung and the thereby produced reduction of its respiratory surface may occasionally result in a marked erythrocytosis according to Massione, who observed in such a case an increase of erythrocytes to 10 million cells and of the hemoglobin content to 150 per cent. A similar observation was reported by Pancoast and Pendergrass, who mentioned that a high erythrocytic count sufficient to suggest polycythemia is frequently associated with pneumoconiosis. The two authors suggested that lung fibrosis and pulmonary arteriolosclerosis can produce a condition akin to polycythemia, presumably due to an impaired exchange of oxygen and carbon dioxide. Distinction has to be made between true polycythemia and the erythrocytosis of compensatory type in lung fibrosis.

VI. ERYTHROCYTOSIS FOLLOWING CONTACT WITH CERTAIN METALS

(Arsenic, Germanium, Manganese, Iron, Antimony, Cobalt, Lead, and Mercury)

Under some circumstances, the occupational and experimental introduction of some metals and their compounds into the body of man or other animals brings about an increase in the number of erythrocytes in the circulating blood. The causative mechanism and the significance of this phenomenon may differ with the substance involved and the quantities entering the organism. These factors in turn influence the biological reaction produced.

Arsenic. Clinical as well as experimental evidence supports the contention that contact with arsenicals may cause an elevation in the erythrocytic level of the blood. The presence of erythrocytotic states in vineyard workers, who, using arsenical insecticides, suffered with chronic arsenical poisoning, have been reported by Dörle and Ziegler; and Schöndorf. A polyglobulosis of 7,675 million erythrocytes was recorded by O'Donovan in a worker with an arsenical dermatosis and epithelioma, who was employed in a sheep-dip plant. Arsenicals, usually in combination with iron compounds, are employed extensively as a therapeutic measure in anemic conditions because of their beneficial effects upon the blood. The causative mechanism active in the production of this effect has remained thus far controversial. While some investigators believe in a direct or indirect, hematopoietic stimulative action of the arsenic, others consider the hematic changes as only apparent ones, resulting from an increased hemo-concentration.

The latter conception is based upon the fact that the introduction of appreciable amounts of arsenic produces a severe irritation of the gastrointestinal tract. This causes severe diarrhea and degenerative lesions in the liver, which, according to our present knowledge of the factors controlling erythropoiesis, do not favor this process. The role which dehydration may play in the production of an erythrocytotic condition in arsenic poisoning was noted by Hueper; and Shumacker and Wintrobe. Evidence supporting this view was presented by Hofmann in experiments carried out on dogs and rabbits which had been given toxic amounts of arsenious acid. The increase in erythrocytes observed in these animals was attributed by Hofmann to an increased hemo-concentration resulting from diarrhea and from vascular congestion, following a paretic action upon the vascular walls. The observations made by Stockman and Charteris on dogs and rabbits treated with arsenic for several months are less definite in this respect since they found a bone marrow of deeper red than normal, a dilatation of the capillaries, and a degeneration of the megakaryocytes, but no appreciable increase of erythroblasts.

Bettmann claimed, on the basis of similar experiments, that the number of erythroblastic cells in the bone marrow was increased. Wichels and Höfer,

also, reported that large doses of arsenious acid are followed by the appearance of numerous reticulocytes in the peripheral blood. They considered this phenomenon as indicative of the stimulating action of arsenic upon the erythropoietic function of the bone marrow. This contention agrees with the findings of Petrányi on dogs, in which the administration of arsenious acid brought about an increase in the number of erythrocytes and the total amount of blood. However, the average volume of the individual red cell was reduced and its resistance to hypotonic saline was diminished.

Germanium. Muller and his co-workers reported that the administration of colloidal solutions of germanium dioxide to rabbits and guinea pigs caused an erythrocytotic increase. Muller attributed the hematic effect of the germanium dioxide to the oxygen carrying power of this compound, which was supposed to stimulate the erythropoietic function of the bone marrow. The observation on the erythrocytotic action of germanium dioxide was substantiated by Hueper; and Keeser; but these investigators could not find any evidence of an increased erythropoietic activity of the bone marrow in their animals. Hueper pointed out that the fundamental conception underlying the erythrocytotic reaction, as propounded by Muller, was incorrect, because a stimulation of erythropoiesis is, in general, the result of a decreased oxygen carrying power of the blood and not an increased one. Hueper stated, also, that animals subjected to repeated injections of colloidal germanium dioxide develop severe diarrhea and exhibit a brownish-red blood, indicating the presence of dehydration and methemoglobin. The reactive phenomena accompanying and causing the erythrocytotic changes in the blood after toxic doses of germanium dioxide resemble closely those seen and evidently active in arsenic poisoning.

Manganese. The occupational exposure to manganese and its various compounds is wide-spread. Considerable contact with manganese dust occurs during the mining of manganese ores—pyrolusite (MnO_2), manganosite (MnO), and pyrochroite ($Mn(OH)_2$)—and during the grinding of these ores. Pyrolusite is used for the production of various manganese compounds (potassium permanganate), for the manufacture of oxygen and chlorine, manganese dyes, lacquers, enamel, marbled soaps, dry cell batteries, alloys with nickel and steel, and as a decolorizing and colorizing agent in glass making.

Several reports indicate that the contact with manganese compounds, afforded during some of the various operations listed above, has been the cause of erythrocytotic reactions in the blood of workers (Martineck). It was observed by Schwarz that eleven out of fifteen manganese workers examined exhibited erythrocyte values ranging from 6.0 to 8.5 million cells in the presence of a normal hemoglobin concentration. A transitory polyglobulia, followed by anemia, was seen by Baader in a worker loading manganese ores. Davis and Huey observed two cases of erythrocytosis with chronic manganese poisoning among workers in a Bessemer steel plant. The erythrocytotic re-

action is characterized by the appearance of polychromasia, basophilic granulations, and other signs of bone marrow stimulation. It has been asserted that manganese compounds aid in the production of hemoglobin when administered with copper and iron (Titus, Cave and Hughes; Titus and Hughes; Lyon-Caen and Jude).

The erythrocytotic action of these substances has been confirmed by numerous observations on animals treated with manganese compounds. An increase in erythrocytes in a female dog fed with a manganese compound was recorded by Debierre. Petrányi observed that dogs exhibited an increase in the quantity of blood, erythrocytes, and hemoglobin after ingestion of a manganese compound. The rise of the hemoglobin concentration lagged behind the increase of red cells. Continued administration of larger amounts of manganese resulted in the development of an anemia and exhaustion of the bone marrow. The occurrence of an initial rise of red cells in rabbits following the administration of manganese carbonate was reported by Caso. After the daily feeding of two grams of pyrolusite to cats, for a period of four weeks, Schwarz and Pagels observed at the end of this interval a rise in erythrocytes ranging from two to three million, and a 10% increase in the hemoglobin concentration. The erythrocytotic reaction produced in one cat by the insufflation of powdered pyrolusite persisted for a period of five months following the cessation of exposure. In another cat the erythrocytes rose from a normal level of 9.5 million to 13.0 million, and the hemoglobin concentration, at the same time, rose from a normal of 75 per cent to 81 per cent. Prolonged treatment with manganese compounds resulted in the development of an anemia. The addition of manganese salts to the milk diet of rats by Marshall resulted in erythrocytic values ranging from 10.5 to 13.0 million as compared with 7.5 to 8.0 million erythrocytes in the control animals. Manganese introduced into the organism must pass rapidly from the blood and be stored somewhere in the body; it is mobilized gradually from these depots and excreted with the feces (Reiman and Minot; and Baader). At no time could Reiman and Minot find an increase in the manganese content of the blood of manganese workers or of dogs which had ingested manganese compounds. In a worker suffering from chronic manganese poisoning and previously employed in loading manganese ores, Baader observed excretion of manganese with the feces for a period of 16 months, after cessation of exposure to manganese.

Iron. Various claims have been advanced that the introduction of iron compounds, the important component of hemoglobin and a close chemical relative of manganese, into the body by different ways may elicit an excessive erythropoietic activity of the bone marrow. Petrányi reported that dogs treated with an iron compound developed an erythrocytosis and plethora. An increased number of nucleated erythrocytes in the spleen, or reticulocytes in the peripheral blood, together with an activated erythropoiesis in the bone marrow and spleen in dogs treated orally or intravenously with ferric ammonium

citrate was observed by Chatterjee. The repeated intravenous administration of a complex sodium salt of ferric tartrate into normal rabbits was followed, Schreiber asserted, by an increase in erythrocytes, leucocytes, and hemoglobin concentration in the blood combined with an appreciable erythroblastic reaction of the bone marrow. An erythrocytotic effect from iron compounds was observed by Beard and Andes during an experimental study on polycythemia.

Keeser did not find any changes of the erythrocytic number and hemoglobin concentration in animals given iron chloride. The administration of iron compounds to man was followed by a rise in reticulocytes from a normal range of 4 to 8 per thousand to 18 to 29 per thousand (Wichels and Höfer), whereas the figures for the hemoglobin and erythrocytes remained unaltered.

From his analysis of the pharmacologic action of iron and its compounds, Starkenstein concluded that they may stimulate a hypofunctioning erythropoietic tissue into increased activity, but that no amount of iron medication is capable of increasing the production of erythrocytes and hemoglobin beyond the normal physiological limit. He conceded that iron compounds may exert, under normal conditions, a minor stimulative effect upon the erythropoiesis, by increasing the amount of erythroblastic tissue in the bone marrow. The transient increases of reticulocytes in the circulating blood (reticulocytic crises) following the introduction of iron compounds do not represent any specific reaction to the iron, according to Starkenstein, as they are seen after the administration of many different substances. Starkenstein pointed out that there does not exist any possibility of chronic iron poisoning which may be the cause of an erythrocytotic reaction, as ferrous iron (which is the biologically active and, at the same time, the labile form) is rapidly oxidized in the blood into the inactive ferric form. According to this argument, iron differs fundamentally from manganese, since the manganous compound represents the active and the stable form.

Apparently no evidence exists which incriminates occupational exposure to iron or iron compounds as the cause of an erythrocytosis, resulting from direct action upon the hematopoietic tissue or the blood (Beintker; and Hendrych and Klimesch). The only reference found relating exposure to iron dust with erythrocytosis was mentioned in relation to the development of an obliterative arteriolar pulmonary sclerosis (Rosenthal). The diffuse fibrosis of the lung which may result from a sidero-pneumoconiosis may cause, in very pronounced instances, such an interference with the respiratory function and circulatory conditions of the lung that a defective oxygenation of the blood ensues, and a compensatory erythrocytosis develops on the basis of an anoxemia. Sidero-pneumoconiosis is seen in workers mining and handling iron ores, and grinding and polishing manufactured iron goods (Stewart and Faulds; Bohrod; and Hart). Exposure to iron ore containing iron oxide causes the red type of pulmonary siderosis; while contact with the metallic

iron dust during grinding and polishing operation causes the black variety of pulmonary siderosis, and mainly represents a silicosis.

Antimony. The occurrence of polyglobulia as a transitory and initial reaction to the exposure to fumes of antimony was reported by Seitz, who observed this phenomenon in type casters and foundry workers. 32 to 35 per cent of the personnel of some type-casting rooms exhibited erythrocytic counts above 5.50 million, while 27.1 per cent had more than 7,500 leucocytes, but the thrombocytes were always decreased. Many of these individuals had a lymphocytosis (lymphocytes above 40 per cent).

Severe antimony poisoning among these workers was characterized by anemia, thrombocytopenia, lymphocytosis, and eosinophilia, in connection with the appearance of normoblasts with degenerated nuclei, polychromasia, and myelocytes in the circulating blood. The bone marrow showed degeneration of the erythropoietic and myeloid tissue. Antimony workers, according to Seitz, show a tendency toward the development of a polycythemia vera. Similar observations were made by the same author in experimental cats and rats, which were given antimony compounds orally, subcutaneously, or by insufflation. In one animal (cat) thus treated the erythrocytes rose in three days from 6.30 million to 8.20 million, followed, after a second and third period of three days each, by a rise to 9.00 and 10.44 million cells, respectively.

Lead. Lead has a toxic effect upon the hemoglobin as evidenced by the appearance of hematoporphyrin in the blood and urine (in cases of lead poisoning), and is selectively stored in those organs which are the sites of hematopoiesis, namely, the bones. The presence of disorders in the blood and blood forming organs is one of the characteristic features associated with occupational lead poisoning. Anemia is associated in general with lead poisoning. It is not well-known that a mild degree of lead poisoning, or the initial phase of a more severe intoxication with this metal, may be characterized by an increase of erythrocytes in the blood ranging from 5.4 to 7.0 million (Otto; Humperdinck; Kost; and Schmidt and Weyrauch). The hemoglobin values vary a great deal and may be decreased or increased (up to 115 per cent) (Kost). This phenomenon, polyglobulia with increased hemoglobin, was successfully reproduced in animals by the administration of small doses of lead (Kogan and Smirnowa).

In lead poisoning the bone marrow shows the direct toxic and stimulative effect of this metal. There is an increase in the number of erythroblasts, proerythroblasts, macroblasts, and normoblasts, while, at the same time, degenerated nuclear forms in erythrocytic cell types are observed, especially in the normoblasts. Early and mild lead poisoning results in a hyperplasia of the erythropoietic tissue. If the toxic action is prolonged or severe, the degenerative processes predominate, and anemia follows. The initial stimulation of the erythropoietic activity of the bone marrow is a response to the more

rapid destruction of the erythrocytes, whose life span is shortened by lead, and is thus of a regenerative nature. Otto expressed the opinion that an increased hemo-concentration caused by an expression of plasma from the spastically contracted vessels, which exist in lead poisoning, contributes to the production of an erythrocytosis (Flury).

Mercury. The occurrence of an erythrocytosis in occupational poisoning by mercury has been recorded (Koelsch and Lederer; and Dunajewsky and Peissachowitsch). The workers in mercury mines have been thus far the most affected group. The causative mechanism active in this instance does not seem to be related to any regenerative response to the known anemiogenic effect of mercury, but is attributed to an increased hemo-concentration following colitis and cachexia. Meyer and Gottlieb observed similar blood changes in animals experimentally exposed to mercury compounds.

Cobalt. At the present it is not known whether occupational exposure to cobalt, its compounds, or ores has ever produced an erythrocytosis in man. The investigations conducted by a commission of the International Bureau of Health of the League of Nations, in connection with the occurrence of pulmonary cancer among cobalt miners in Schneeberg, have not yielded any information upon this question. In view of the existing uncertainty as to the erythrocytotic activity in man, it was thought advisable to record the experimental evidence attesting to the erythrocytotic effect of cobalt salts.

Among the first investigators to record the erythrocytotic action of cobalt were Waltner and Waltner, who fed rats a diet containing 0.5 per cent cobalt chloride for a period of five to six months. They observed erythrocyte values up to 10.5 million and hemoglobin concentrations of 165 per cent. At this time the animals showed a loss of fertility, impairment in growth, and porosis of the bones. A diet containing cobalt nitrate produced a similar effect upon the erythrocytic picture. The leucocytes were not altered, either quantitatively or qualitatively, during these dietary experiments. The addition of smaltine (a cobalt arsenide ore, As_2Co, containing approximately 15 per cent iron) did not produce any blood changes in spite of the fact that this ore contains three substances, cobalt, arsenic and iron, which under proper conditions exert an erythropoietic stimulation.

Marshall was successful in eliciting an erythrocytotic response in rats treated with cobalt compounds. Adult rats fed cobalt chloride (Pitini and Messina) showed an elevation in erythrocytes ranging from the original level of 8.5 million to 12.0 to 13.0 million, while the hemoglobin concentration rose from 13.5 grams to 18.0 to 20.0 grams per 100 cc. blood. Dogs, cats, and rabbits receiving the same medication had, after some time, hemoglobin values which surpassed the original level by approximately 13 per cent. Erythrocytotic responses after cobalt administration were observed in dogs by Mascherpa and Davis; the latter gave a 1:1000 solution of cobalt chloride by a stomach tube every day for two weeks, and obtained a 20 per cent increase in erythrocytes.

Cobalt polycythemia in adult rats was obtained by adding one per cent cobalt chloride to the diet (Myers, Beard, and Barnes). Similar observations were made on rats by Stare and Elvehjem; Brand and Stucky.

The addition of manganese to a diet containing cobalt tended to keep the erythrocytosis at a high level for a more extended period than when cobalt alone was given, and decreased the toxicity of the cobalt, according to Orten, Underhill, Mugrage, and Lewis. These authors demonstrated that the erythrocytic increase caused by the introduction of cobalt is not the result of an increased hemo-concentration, but represents an actual increase in the number of erythrocytes and the blood volume. This contention was confirmed by observations of Kleinberg, who found in rabbits, after repeated subcutaneous injections of cobalt chloride, an increase of erythrocytes and especially reticulocytes. The feeding experiments of Beard and Andes, performed with rats, showed that the polycythemic action of cobalt does not depend upon the simultaneous presence of copper in the diet. The conclusion was reached by Hendrych and Weden that cobalt, just as nickel and copper, stimulates erythropoiesis; but it is without influence upon the production of hemoglobin, since these three metals are incapable of replacing iron in the hemoglobin molecule. The production of hemoglobin is not influenced by cobalt, nickel, or copper, even in the presence of an activated erythropoiesis, if the diet is deficient in iron.

While the morphologic change occurring in the blood under the influence of a cobalt medication resemble those found in polycythemia vera, the erythrocytotic response elicited by cobalt is only a transient one and fades within 10 days following the arrest of the exposure.

VII. ERYTHROCYTOSIS IN PHOSPHORUS POISONING

During the last thirty years there was a considerable decrease in the occupational, accidental, and suicidal incidences of phosphorus poisoning due to the adoption of legislative measures, in the majority of countries, prohibiting the use of white phosphorus in the manufacture of matches (Oliver). Reports dealing with the occurrence of erythrocytosis in phosphorus poisonings go back to the turn of the last century, when poisonings of this kind were relatively common (v. Jaksch; Silbermann; Taussig; Norgren; and Pisarski). From a series of 118 cases of phosphorus poisoning, Silbermann noted that erythrocytic values from 5.0 to 6.0 million were present in 44 cases, from 6.0 to 7.0 million in 20 cases, 7.0 to 8.0 million in 11 cases, and in three instances 8.0 million was surpassed. A leucocytosis existed in a considerable proportion of these cases; in 38 cases the white cells ranged from 8,000 to 12,000, in 6 cases from 12,000 to 15,000, and in 11 cases above 15,000 cells. On the other hand, thirteen cases exhibited a leukopenia below 5,000 cells.

The successful production of phosphorus erythrocytosis experimentally in dogs was carried out by Taussig; Pisarski; and Welsch. The latter ascribed

the erythrocytosis observed to an increased hemocentration. This conception was favored by Shumacker and Wintrobe, who based their opinion upon the development of an erythrocytosis in dogs treated with hepatotoxic carbon tetrachloride. These authors suggested that the erythrocytosis found in poisonings with hepatotoxic substances, such as phosphorus, arsenic, and carbon tetrachloride is not the result of a stimulating effect exerted by the injured liver, but represents the product of a dehydration caused by the presence of diarrhea. This explanation is not applicable to all instances of phosphorus erythrocytosis occurring in man and animals, as both diarrhea and vomiting may be absent and, therefore, cannot be incriminated as the causative erythrocytotic mechanism. v. Jaksch has pointed out that there is not a change in the protein content of the blood and its specific gravity, thus refuting the dehydration theory. As there is an increased excretion of bile pigments in phosphorus poisoning indicating an increased erythrocyte destruction, it appears probable that this factor may account, in part, for the erythrocytotic stimulation of the erythropoiesis of the bone marrow.

VIII. ERYTHROCYTOSIS FOLLOWING THE INTRODUCTION OF GUM-SHELLAC

Instances of occupational erythrocytosis following exposure to gum-shellac are not on record. The constantly increasing use of spray-guns to apply lacquers and paints containing shellac provides greater opportunities for an intense inhalation of this substance (in the form of a mist). As parenteral introduction of shellac into experimental animals has demonstrated that this material can exert a powerful erythrocytotic action, it was considered advisable to report these observations briefly (Otto; and Muller).

From a chemical viewpoint shellac consists mainly of aleuritic acid ($HO \cdot CH_2 \cdot (CH_2)_5 \cdot CH(OH) \cdot CH(OH) \cdot (CH_2)_7 COOH$) together with red coloring matter, wax, and water. It is an amber secretion from trees of the acacia family growing in India, produced by an injury caused by a species of insect. Gum-shellac is a powerful protective colloid, and when introduced alone into the organism it is quite toxic. It loses much of its original toxicity, when bound to colloidal carbon particles (India ink). Muller injected rabbits with a brand of India ink containing gum-shellac as protective colloid. After several intravenous injections there was a marked erythrocytotic response characterized by the appearance of large numbers of nucleated red cells in the circulating blood (60,000 to 70,000 normoblasts and erythroblasts per cmm.). This was attributed to an increased release of immature red cells from a hyperplastic bone marrow, which showed an accumulation of nucleated erythrocytes in the intersinusoidal capillaries.

b. Physical Agents

I. ERYTHROCYTOSIS FOLLOWING EXPOSURE TO ACTINIC AGENTS

The assertion that exposure to certain actinic agents (ultraviolet rays, roentgen-rays, and rays emitted from radioactive substances) may cause, under

proper conditions, the development of erythrocytotic reactions is supported by Harrop and Wintrobe; Koelsch; and Selling and Osgood). That a transitory erythrocytosis and leucocytosis are characteristic for the early hematic reaction in occupational exposure to roentgen-rays, while leukopenia and anemia represent the late manifestations has been stated by Koelsch. Carman and Miller observed that radiologists may show a slight increase in erythrocytes and color index. Exposure to small doses of roentgen-rays or radioactive substances (thorium emanation) was noted by Lambin as the cause of polyglobulia, which, in several cases, attained values up to 6.9 million cells; however, continued contact with these agents may result in a drop in the number of erythrocytes. Similar observations were recorded by Cluzet and Chevalier; Pfahler; Lavedan; Hamperl and Roemheld. Gudzent and Halberstaetter reported that they did not see any changes in the red cell picture in radiologists; while Mottram noted the presence of an anemia in individuals exposed occupationally to actinic agents.

In view of these controversial contentions, Moldawsky reinvestigated this question by studying the blood of the personnel of several therapeutic radiation institutes and commercial radium laboratories in Berlin. Moldawsky found that there was a considerable increase in the number of reticulocytes in the majority of the exposed individuals examined (4 to 24 reticulocytes per 1000 cells instead of 1 per 1000 normally), and the effect was least pronounced in individuals in contact exclusively with radioactive substances. The degree of the reticulocytic increase ran parallel to the time of exposure and continued for more than four weeks after the cessation of contact with actinic agents. In two out of nineteen persons studied there were moderately increased erythrocytic figures (5.86 and 5.65 million erythrocytes). This author concluded that the bone marrow of these radiologists and related workers was hyperactive, and that this condition started soon after the first contact with the actinic agents. He suggested that the presence of bad air (lack of oxygen) in the workrooms may have contributed to the production of the blood reactions observed. Auler mentioned that a physician studying by serial examination the blood of the workers employed in the Auer-Werke and exposed to thorium-X, observed erythrocytoses up to 8.0 million cells. Lacassagne noted that small amounts of radioactive substances may cause a leucocytosis and a polyglobulia. A similar statement was made by Laborde, who cited Lavedan in support of his opinion (Laborde; and Leclercq). A hematological survey of the personnel of the anticancer centers of Marseilles by Cornil and Rouslacroix brought out the fact that there was a tendency to polyglobulosis in 20 per cent of the attendants of the radiation departments (in 8 out of 40 cases) (5.45 to 6.35 million erythrocytes, and up to 120 per cent hemoglobin). In a case of acute, fatal thorium-X poisoning Hamperl and Roemheld noted that the number of erythrocytes rose from 5.1 million at the beginning of the poisoning, to a range of 6.5 to 7.0 million shortly before death. Considering that a hemorrhagic colitis was coexisting as a result

of the poisoning, the erythrocytic rise observed in this instance is evidently not an actual one, but related to an increased hemo-concentration.

In this connection the observations of Tönges and Kalbfleisch; Kalbfleisch; and Doenecke, upon several workers in commercial radium laboratories who succumbed to a fibrosis of the lung resulting from a chronic occupational radium injury, are of interest. Doenecke reported that one of these cases had 5.4 million erythrocytes and 102 per cent hemoglobin at a time when there was definite evidence of radium poisoning. The bone marrow examination on the other two cases at autopsy showed numerous immature nucleated erythrocytes indicating an increased erythropoietic activity of this tissue in the presence of a lowered myelopoiesis. It is doubtful whether these marrow changes can be ascribed to the action of the radioactive substances in the tissues of these workers, as they were suffering from a generalized fibrosis of the lung. This interfered with proper respiration and pulmonary circulation and caused a status of relative anoxemia, known to be a powerful erythropoietic stimulant. The bone marrow of a chemist dying from radium and mesothorium poisoning was studied by Reiter and Martland, and their findings indicate that even in the presence of a marked toxic anemia the hematopoietic tissue of the vertebrae may show a very marked hyperplasia of the erythropoietic elements (closely packed megaloblasts, normoblasts, and erythrocytes, and almost complete absence of myeloid cells). This observation demonstrates again that radiating energy may exert a marked regenerative stimulus on the erythropoietic elements of the bone marrow.

The erythrocytotic effect of exposures to radiating energy was confirmed by experimental investigations of several workers. An increase in erythrocytes from the original value of 4.7 to 6.7 million was obtained by Lazarus after administration of 300 E.S.U. radiothor, an effect which he considered as evidence of a bone marrow stimulation. Increases of erythrocytes up to 8.3 million were observed by Brill and Zehner following the injection of radium chloride solution (0.002 to 0.07 mg. radium element) into dogs and rabbits. Similar transitory erythrocytotic changes (up to 6.8 million) were noted by Lacassagne, Lattés, and Lavedan in rabbits injected intravenously with 100 to 500 electrostatic units of polonium, which emits a pure alpha radiation. A polyglobulia was found by Heinecke in rabbits irradiated repeatedly with roentgen-rays. Seventy per cent of the rabbits exposed over the lumbar vertebral region (with the rest of the body shielded) to roentgen-rays developed an erythrocytosis, while 30 per cent revealed a decrease in erythrocytes or remained stationary (Krömecke). The increase in erythrocytes occurred during the first few days (three to four) of treatment, and the rise ranged from 10 to 28 per cent above the original level regardless of the amount given. Fragility tests on the blood of these animals did not show increased resistance to hypotonic salt solution, thereby suggesting that appreciable numbers of young erythrocytes were not present, such as is observed

in phenylhydrazine poisoning, where this reaction is strikingly positive and characteristic for this reason (Hueper). The examination of the bone marrow of the rabbits used did not reveal any evidence of an increased erythropoietic activity. Krömecke is inclined to consider the erythrocytotic response as the result of a distributory shift of the red cells and not as the result of an actual proliferative increase.

Lavedan; and Holthusen ascribed the polyglobulia, appearing after irradiation with roentgen-rays, to an increase in hemo-concentration. Since the same amount of radiating energy may produce erythrocytosis in some individuals and anemia in others, Lavedan suggested that idiosyncrasy may account for the occurrence of such discrepancies. This idea deserves further consideration in future studies, as observations made during recent years with certain chemotoxic substances (amidopyrine, sulfanilamide, and aromatic arsenicals) demonstrated that the same substance and dosage may cause blood reactions of an apparently allergic nature differing widely, however, in type (agranulocytosis, leukemoid leucocytosis, aplastic anemia, and myelophthisis).

Apart from this possibility which may influence the reaction observed in the individual case, the most probable explanation of the differences recorded seems to be related to the time of observation and the duration of exposure. The initial erythrocytic increase observed during the first three to four days after the first exposure to radiating energy is likely to be of a distributory origin (Koelsch; and Krömeke). This mechanism cannot account for the sustained erythrocytoses observed as the result of prolonged exposure to the radiating agents, especially as they are accompanied by an increase of reticulocytes in the circulating blood. An excessive regenerative hyperplasia of the bone marrow, such as existing in the cases of radium poisoning mentioned, appears to be the underlying cause of the erythrocytotic reactions in such instances.

II. TRAUMATIC ERYTHROCYTOSIS

Accidental injuries are, in general, more apt to cause anemia through loss of blood, than to result in an increase of the red elements in the blood. There exist three different types of traumatic conditions which may become the cause of the traumatic kind of erythrocytosis:

a. Injuries to the chest and neck impairing the proper ventilation of the lung and resulting in a deficient oxygenation of the blood (Zadek), penetrating wounds of the chest wall producing a pneumothorax, and injuries which cause an obstruction of the trachea belong to this group of traumatic erythrocytotic agents.

b. Injuries which result in a prolonged loss of small quantities of blood may become the source of an erythrocytotic reaction (Otto; and Naegeli). For example, a traumatic activation of a chronic gastric ulcer may assume such a causative rôle. There is an excessive formation of young erythrocytes asso-

ciated with this response, as the number of reticulocytes is elevated appreciably.

c. Injuries to the spleen, which affect the splenic parenchyma directly or produce this effect indirectly by circulatory disturbances in the splenic vessels (thrombosis of splenic vein), may be followed by an increase in erythrocytes. This possibility is suggested by occasional observations made when a marked polyglobulia was noted after the surgical removal of the spleen (Kretz; Weinert; Brieger; and Kuttner). The occurrence of an erythrocytotic reaction as a sequela of a thrombosis of the portal or splenic vein was reported by Bock and Frenzel. From this and additional clinical and experimental evidence, they concluded that the spleen influences the numerical erythrocytotic status of the blood not only by being a store-house of the erythrocytes and being active also in their destruction, but by exerting a direct inhibiting influence upon the proliferative activity of the erythropoietic tissue in the bone marrow. A partial or complete traumatic elimination of this organ may delay the normal destruction of erythrocytes, and remove, at the same time, a physiologic brake upon the erythropoiesis, causing a temporary erythrocytosis.

3. POLYCYTHEMIA VERA

A. Trauma and Polycythemia Vera

The interrelations which may exist between a trauma and a polycythemia vera may be of two different kinds. The trauma may be superimposed upon a preexisting polycythemia vera, and thus influence its course and outcome by causing unfavorable complications, such as thromboses and hemorrhages, for which the polycythemia produces a predisposing soil; or the trauma may affect a normal individual and elicit a primary hematopoietic reaction, which ultimately assumes the character of a polycythemia.

Cases of the first mentioned variety have been reported by Jacobi; Stursberg; Hecht and Weil. The communication of Jacobi is of special interest in this connection. The patient died from a mesenteric venous thrombosis complicating a polycythemia vera, after suffering from two to three years before the present illness from a phlebitis of the leg, following an injury to that extremity. Since the autopsy showed that the phlebitic process of the leg had become completely inactive, it may be taken for granted that no causative interrelation existed between the old healed thromboses of the varicose veins of the legs and the fresh thromboses of the mesenteric vessels. The occasional spontaneous occurrence of mesenteric thrombosis and portal thrombosis and polycythemia vera (Seggel) demands great caution in assuming the existence of any causative interrelations of a traumatic nature. Isaac conceded the possibility that accidental injury, infection, or some other type of exogenous agent may exert an aggravating effect upon a preexisting polycythemia. Such a conclusion was reached by Stursberg in the analysis of his case.

There is only one case on record for which the claim is made that a preceding trauma was the cause of a polycythemia which appeared afterwards (Zadek). During the war in 1917 the patient received a gunshot wound which caused a distortion of the spine. Approximately six years later he was treated in the hospital for an abscess of the neck, and apparently at that time no symptoms of any kind suggested the presence of polycythemia. One year later he suddenly became ill with colicky pains in the gastric region. The blood examination showed the existence of a dyscrasia diagnosed as polycythemia vera (8.58 million erythrocytes, 141 per cent hemoglobin, color index 0.89, 0.5 reticulocytes per 1000 red cells, an absence of megaloblasts, normoblasts and polychromasia, 77,400 platelets, 5,000 leucocytes, 8.4 per cent polymorphonuclear neutrophiles, 11.2 per cent lymphocytes, and 4.8 per cent mononuclears). A smear made from the marrow of the sternum revealed the presence of numerous megakaryocytes and mainly orthochromatic erythrocytes. The abdominal symptoms subsided slowly and the leucocytic shift to the left decreased at the same time. There was a reduction in size of the previously enlarged spleen and liver, but the number of erythrocytes was still increased markedly. At this time it was assumed that the entire process was probably not older than nine months. Upon reexamination three years later the erythrocyte count was normal (5.10 million), the hemoglobin concentration was 104 per cent, the leucocyte count was 3,800, the spleen was small, and the liver was still somewhat enlarged. A roentgen-ray picture taken of the chest at that occasion showed an old fracture of the tenth and eleventh rib and a scoliosis of the spine. Six years after the polycythemic episode his condition was essentially normal with the exception of a moderate leukopenia (4000 to 5000 leucocytes). The hyperbilirubinemia which had been present during and for some time after the polycythemic attack had disappeared.

In commenting upon these observations Zadek conceded that the remissions occurring in the Vaquez disease are not as prolonged as that seen in his case. He is convinced that a causative relationship exists between the war trauma, the thrombosis of the splenic vein, which apparently existed during the acute abdominal attack, and the polycythemia vera. He referred, in support of his contention, to a case of traumatic thrombosis of the splenic vein recorded by Severin.

In a critical analysis of this case it becomes apparent that there are several points in the observations which cast serious doubt upon the correctness of the clinical diagnosis upon which the argument is based. The absence of immature and nucleated erythrocytes, the low number of thrombocytes, and the presence of a leukopenia do not favor the diagnosis made. The blood picture resembles closely that observed by Kretz after splenectomy (polycythemia coupled with leukopenia and thrombopenia). It was pointed out, also, in the preceding discussion of traumatic erythrocytosis, that thrombosis of the

splenic or portal vein, or the existence of a cirrhosis of the liver (Seggel) may result in a transitory increase in the erythrocytes. The subsequent marked reduction of the spleen and the apparently permanent remission of the blood changes favor a different interpretation of this case, too. It appears possible or even probable that the conditions set up in the splenic region by the war injury may have caused the thrombosis of the splenic vein. This did not result in a polycythemia vera, but produced an unusually marked and prolonged erythrocytotic response. These considerations permit the conclusion that thus far not a single reliable and acceptable case of a genuine traumatic polycythemia vera has been placed on record.

B. Experimental Polycythemia Vera

Recently experimental evidence has been obtained which indicates that the introduction of tar, or one of its carcinogenic components (3.4-benzpyrene), into the marrow cavity of rat femurs can produce polycythemic or erythroleukemic conditions (Bernard; and Storti and Storti). Erythrocytic counts up to 16.0 million cells were noted by Bernard within 25 days after the beginning of repeated injections of tar dissolved in olive oil. There were numerous erythroblasts (up to 75 per cent among the nucleated cells), reticulocytes, polychromatophilic, anisocytic, and poikilocytic cells. These changes were not of an acute transitory nature but were of the chronic type, and persisted for several months. In some of the animals a more or less marked leucocytosis developed at a later time (110,000 per cmm.). The bone marrow contained densely crowded, immature erythrocytic and myeloid cell forms, presenting a picture similar to that seen in human erythro-leukemia. Similar observations were made by Storti and Storti following the intrafemoral injection of 3.4-benzpyrene into rats. They stated that the evidence suggests the possibility that constitutionally predisposed individuals whose bone marrow comes in direct contact with certain carcinogenic substances may respond with blood-and tissue reactions of the erythremic, leukemic, or erythro-leukemic type. Numerous reports noted the apparent transition of polycythemic into erythroleukemic conditions in man. Some authors even asserted that the myeloid reactive component usually present in polycythemia to a degree is the more important feature of the disease (Weber; Kraus and Schiller; Dameshek; and Schwarz).

4. GENERAL CONCLUSIONS ON ERYTHROCYTOTIC REACTIONS

The etiology and mechanism of relative and distributory erythrocytoses have been presented. These conditions are, in this connection, only of significance inasmuch as they may present the problem of differential diagnosis from actual erythrocytoses, and in view of the fact that they may complicate or contribute to erythrocytotic reactions of the latter type.

The causative mechanism underlying the various types of actual erythrocytoses presented varies with the genetic agent active. Different kinds of stimuli may be elicited at the same time by the same agent, and may combine in producing the erythrocytotic response. The following compilation may aid in clarifying this statement.

Causative Mechanisms Present in Actual Erythrocytoses

I. Functional blood anoxemia produced by defective oxygenation of this tissue resulting from
   a. inhalation of air with a lowered oxygen tension (high altitude);
   b. circulatory disturbances of the lung, preventing proper oxygenation of the blood passing through the lungs in the presence of sufficient oxygen in the inhaled air (obliterative pulmonary arteriolosclerosis and fibrosis of the pulmonary tissue);
   respiratory disturbances affecting the lung tissue (pneumothorax);
   c. presence of a pathologic hemoglobin lowering the oxygen carrying power of the blood (carbon monoxide hemoglobin, sulfhemoglobin, and methemoglobin).

Hematogenic anoxemia represents one of the most powerful erythropoietic stimuli of the bone marrow.

II. Anemiogenic agents which exert a cytotoxic effect upon the circulating erythrocytes, the bone marrow and/or the liver. The direct erythrocytotic agents are hemolytic substances such as phenylhydrazine and saponin. Other substances, such as benzol, roentgen-rays, and radioactive materials, act directly upon the proliferative activity of the bone marrow; while phosphorus and arsenic bring about hepatic injury. The appearance of an erythrocytotic effect in response to these agents evidently depends on the possibility of an excessive, regenerative, erythropoietic activity. This, in turn, is dependent upon exposure to small amounts of these anemiogenic agents combined with a proper interval between individual exposures, permitting an adequate regenerative reaction. An erythropoietic stimulation of this kind exerted over too long a period of time may end ultimately in exhaustion of the erythropoietic function with the development of an anemia. The same result may occur if the too prolonged exposure is accompanied by a cumulative effect of the agent, causing a predominance of the injurious action upon the erythropoietic tissue over the regenerative stimulus. Erythrocytoses produced by the various metals mentioned seem to take this course. It is doubtful and controversial, whether any of the erythrocytotic agents included in this group can exert, when acting in minute doses, a direct erythropoietic effect upon the bone marrow without causing an injurious effect upon this tissue.

III. A partial or complete elimination of the spleen, by direct traumatic destruction of the splenic parenchyma or a traumatic thrombosis of the splenic vein, may cause a delay in the normal rate of erythrocytic destruction, and

diminish the braking effect the spleen is supposed to exert upon the erythropoietic activity of the bone marrow. Both factors would tend to effect an increase of erythrocytes in the circulating blood.

The rôle which physical and chemical exogenous agents, used industrially and medicinally, play in the increased incidence and production of several of the most serious erythrocytic blood dyscrasias is illustrated strikingly in the material presented above, and supplemented by experimental observations made in recent years. This indicates the necessity for thorough investigations of occupational erythrocytoses for their possible polycythemic potentialities, and for a detailed study of the cryptogenetic polycythemias to determine the possible involvement of occupational etiological factors. Special emphasis in such studies should be placed upon the type, dose, and duration of exposure to erythrocytotic agents as well as to differences in individual reactivity. Careful consideration should be given to all those exogenous occupational agents which may set up, in individuals exposed to them, functional and morphologic organic disturbances, which have been related tentatively to the etiology of polycythemia vera. These are hyperplasia and proliferative hyperfunction of the erythropoietic tissue combined with maturation arrest of megaloblasts (Isaacs); overproduction of the intrinsic gastric principle of Castle (Hitzenberger; Oerting and Briggs; Étienne, Vérain and Louyot; and Schiff); and arteriolosclerosis of the bone marrow, which causes anoxemia and fibrosis of this tissue and stimulates the production of compensatory, regenerative, excessive proliferation of heterotopic erythropoietic tissue (Reznikoff).

It may be of value to utilize an observation made by Seyderhelm for the differential diagnosis between polycythemia vera and toxic erythrocytoses. This investigator found that the hematocrit values in polycythemic polyemia are above 60 per cent because of a predominance of the corpuscular increase in total volume and in individual cell volume over the increase in the amount of plasma. The hematocrit value in erythrocytotic polyemia approaches the normal level of 45 per cent, as there is a more equal increase of the cellular and plasmatic component parts.

5. OCCUPATIONAL AND ACCIDENTAL LEUKOBLASTOSES AND LEUKOBLASTOMAS

A. General Aspects and Classification

The proliferative manifestations of the various component parts of the leukopoietic tissue (reticular and reticulo-endothelial cells, myeloid cells, and lymphoid cells) present a great variety of disease conditions ranging from simple hyperplasias to neoplasms of the most malignant type. The existence of an unusually large number of typical and atypical intermediary forms between the two extremes mentioned, and the apparent occurrence of transitions between certain types are in part responsible for the fact that none of the classifications proposed for these disorders have met with general approval.

The lack of adequate and reliable clinical and pathological distinctive reactions essential for the proper characterization and delineation of the leukopoietic growth reactions has proven to be an especially disturbing factor in the differential diagnosis of conditions differing fundamentally from each other in their respective biologic behaviour (Müller; Krumbhaar; Kracke and Garver; Heck and Hall; and Fitz-Hugh).

The mononucleoses of the blood, which occur with some infections and occasionally during the course of idiosyncrasies to certain drugs (amidopyrine, arsphenamine, benzene, quinine, and sulfanilamide) are, in some instances, of such a type and degree that they are almost indistinguishable hematologically from those associated with acute stem cell or lymphatic leukemia (Fitz-Hugh; Kracke; McKinlay; Downey and Stasney; and Hueper). The clinical and histological differentiation between some hyperplastic, leukemic, and neoplastic growth reactions of the lymphoid organs is at times beset with such difficulties, that even the ultimate course of the disease or the necropsy findings may not establish a definite diagnosis in all these cases (Decker and Little; Brill, Baehr and Rosenthal). The leukopenic changes of the blood and the hyperplasia of immature myeloid cells of the bone marrow (maturation arrest), existing frequently in agranulocytosis of an allergic nature, may resemble those found in myeloid aleukemia (Custer; Fitz-Hugh and Krumbhaar; Piersol and Steinfeld; Gutzeit; and Hueper). The existence of myeloid leukemia may be simulated by leukemoid hyper-leucocytoses and extensive medullary and extramedullary myeloid infiltrations of certain organs occurring in occupational chemical poisonings and several acute and chronic infectious diseases, such as septicemia, vaccination against typhoid fever, erysipelas, scarlet fever, malaria, and tuberculosis. (Feldman and Stasney; Ryan and Medlar; Schultz; Brugsch and Naegelsbach; Arneth; Ziegler; Custer and Crocker; Downey, Major and Noble; Gingold; Wiechmann; Krumbhaar; Heck and Hall; Gudzent; Füchtner; Nägeli; Geissler and Wurm; Roth; Schilling; and Ecke.

An activation of a chronic myeloid leukemia by tuberculosis was observed by Fischer and Lenhartz. Several authors maintained that some of these aforementioned diseases (septicemia, malaria, and tuberculosis) may act as a direct or indirect cause of true leukemic dyscrasias (Sternberg; Mayer; and Cherry). Hematic as well as organic leukemoid reactions may accompany some non-infectious ailments, such as polycythemia vera, Hodgkin's disease, pernicious anemia, familial hemolytic jaundice, erythroblastic anemia, regenerative anemia, carcinosis of the bones, osteosclerosis, and Albers-Schoenberg disease (Falconer; Roth; Heck and Hall; Hueper; Minot and Buckman; and Pendergrass and Pancoast). The occurrence of leukemoid blood reactions in cases of mustard gas poisoning was observed by Krumbhaar. Recognition of the leukemoid character of such complications may present serious diagnostic obstacles (Hill), as true leukemia may coexist with some of these diseases.

The simultaneous occurrence of carcinosis and leukemia is relatively common in mice (Simonds; Hueper; and Slye), while this combination is rarely met in man (Sonnenfeld; Marischler; Mettier and Rusk; and Kugelmeier). Similarly, osteosclerosis and leukemia may coexist (Asmann; Mettier and Rusk; Goldzieher; and Jacobsen). While osteosclerosis usually develops during the course of the leukemic condition as the result of an irritation of the endothelial tissue, it occasionally precedes the leukemic state.

The symptomatic and morphologic difficulties represent only a part of the perplexing aspects, which surround the growth manifestations of the hematopoietic tissue in general and its leukopoietic portion in particular. The controversy regarding the histogenetic derivation of the various types of blood cells has contributed to the existing confusion. The significance of this dispute is of a scientific and practical character.

The scientific interest centers around the question, whether the different blood cells originate from a single stem cell (monophyletic theory) with pluripotentialities, which may be realized in any one of the several cellular forms, or from several histogenetically distinct stem cells, each of which possesses only one specific developmental potentiality (polyphyletic theory). The correlation hypothesis concerning the genesis and causative mechanism active in the different types of leukemias, developed some time ago by Ziegler and recently revived by Wiseman, Doan and Erf, is based on the polyphyletic theory of leukopoiesis. It is assumed in this hypothesis that a disturbance of the equilibrium, allegedly existing under normal conditions between the different types of blood cells, may develop under pathologic circumstances, characterized by partial or complete suppression of one cell type by some toxic agent, into an antagonistic proliferative competition through the thereby effected release of the growth potencies of another cell type. The excessive growth of one cell type may acquire ultimately a leukemic nature (myeloid-lymphoid antagonism).

The principal scientific and practical importance of this conception lies in the implied assertion as to the existence of differences in the reactivity of various blood cells to specific chemical and physical stimuli and noxae. It is a long debated question, whether certain hematotoxic agents may exert an injurious effect upon only one specific type of blood cell or may elicit reactive manifestations in several types of hematic cells, depending upon the presence of some associated exogenous and endogenous conditions.

Several observations made during recent years, especially in connection with allergic reactions to certain drugs [containing a benzene group (Kracke and Parker)] and important industrial chemicals, have proved definitely that the same chemical substance may actuate blood reactions of a diverse type (Fitz-Hugh; and Rhoads). The following enlightening compilation which embodies the various hematic responses thus far observed in connection with several chemicals, was published by Fitz-Hugh:

Drugs Which May Cause Acquired Hematologic Sensitivity

1. Acetanilid			II			11. Gold salts		I			III	IV		
2. Amidopyrine			II	III	IV	V	12. "Neostibosan"					IV		
3. Antipyrine			II				13. "Nirvanol"					IV		
4. Arsphenamine	I	II	III	IV	V		14. "Noveldine"					IV		
5. Benzene	I	II	III	IV	V		15. Phenacetin					IV		
6. Bismuth			III	IV			16. "Plasmochin"					IV		
7. "Causalin"				IV			17. Quinine			II	III	IV	V	
8. Cinchophen				IV			18. "Sedormid"				III			
9. Dinitrophenol				IV			19. Sulfanilamide	I	II	III	IV	V		
10. Ergot			III											

Hematologic Disorders Sometimes Caused by Drug Sensitivity
(Arabic numbers refer to drugs; Roman numerals to diseases)

I. Aplastic anemia:	4, 5, 11, 19.
II. Hemolytic anemia:	1, 2, 3, 4, 5, 17, 19.
III. Thrombocytopenic purpura:	2, 4, 5, 6, 10, 17, 18, 19.
IV. Agranulocytic angina:	2, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 19.
V. Leukemoid reactions:	2, 4, 5, 17, 19.

The tabular data clearly demonstrate that the same chemical agent may act upon different cells of the hematopoietic tissue, and may elicit responses of hypoplastic as well as hyperplastic character. The nature of these responses depends upon the dose, length of exposure, constitution of the individual, and phase of the reaction, in addition to other conditioning endogenous and exogenous factors of a more or less undetermined character (hormones, vitamines, associated injury to liver or spleen, trauma, and fatigue) (Fitz-Hugh). Witts, in his analysis of these blood reactions, considers seriously the possibility that true leukemias may be etiologically related to drug sensitivity. A similar conclusion may be drawn from an opinion expressed by Schilling, who stated that a leukemia may follow upon a primary stage of aplasia, as recent observations have shown that aleukias may become transformed into leukemic conditions. The hematopoietic tissues are evidently very sensitive in their reactions (division, maturation, and emission of cells). Many gradations and transitions may occur within these reactions. A granulocytopenia and an aleukemic leukemia may represent the same, that is, the first stage of a disturbance of the bone marrow, of which the acute myeloblastic leukemia may be the second stage (Voth). This conception corresponds with claims made by Swirtschewskaja, that idiopathic myeloses and myeloid infectious reactions have the same background.

For the proper evaluation of such potential interrelations it is unfortunate that leukemias still occupy a controversial position among the growth reactions of the leukopoietic tissue. While some investigators insist that they

represent proliferative manifestations of neoplastic nature, others are equally emphatic in denying them such character, and allotting to them a position intermediary between hyperplasias and blastomas.

Very little definite and reliable information is available in regard to the etiology of the great majority of proliferative reactions of the leukopoietic tissue, especially those of leukemic and blastomatous types. Consequently, it becomes obvious that any classification and, in turn, the general understanding of this group of dyscrasias must suffer from the uncertainty which exists concerning their symptomatology, morphology, histogenesis, and causative mechanism and etiology. If, in spite of these obvious difficulties, a classification is presented, it is done so with full cognizance of the unavoidable limitations and defects which must accompany such a procedure. Some kind of systematic arrangement of these diseases is essential for the ordered presentation and better understanding of the interrelations existing between occupation and various proliferative reactions of the leukopoietic tissue.

The classification is based on morphologic and biologic characteristics.

A. Benign, transitory, and hyperplastic reactions:
   Lymphoid tissue:
      a). Simple hyperplastic lymphomatosis.
      b). Giant follicular hyperplasia of lymph nodes.
   Myeloid tissue:
      a). Simple hyperplasia of the bone marrow with or without leucocytosis or with leukopenia.
      b). Hyperplasia of the bone marrow with heterotopic myeloid foci.
      c). Atrophy of the bone marrow with compensatory heterotopic myeloid hyperplasia.
      d). Megakaryocytosis.
   Reticulo-endothelial Tissue:
      a). Reticulo-endothelial hyperplasia.
      b). Monocytosis.

B. Progressive, persistent, and blastomatoid reactions (leukoblastoses):
      a). Leukemias (acute and chronic myeloid, lymphoid, mononuclear, megakaryocytic, and erythroleukemic).
      b). Aleukemias.
      c). Multiple myelomas.
      d). Chloromas.

C. Progressive, persistent, and blastomatous reactions (leukoblastomas):
      a). Leucosarcomas.
      b). Lymphosarcomas.
      c). Retotheliosarcomas.
      d). Chlorosarcomas.
      e). Ewing's reticular sarcomas of bones.

Many of the recent advances in our knowledge of anemic conditions have come from occupational and medicinal toxicology, dealing with such diverse conditions as chronic benzene poisoning, toxemia of amino- and nitro-derivatives of aromatic compounds, lead hazards, injuries resulting from exposure to roentgen-rays and radioactive substances, and similar industrially important and medicinally used agents (Lancet). Accumulative evidence, during late years, suggests the possibility of a similarly important rôle, which investigations of the occupational leukopoietic hyperplasias may play in regard to the elucidation of the causation and developmental mechanism of the cryptogenetic leukoblastoses and leukoblastomas. The urgent need of such studies is emphasized by reports concerning the sudden and rapid increase of leukemias during the last fifteen years.

Curschmann observed, in the university clinic in Rostock, that this disease, relatively rare (one case among 1,000 hospital patients) in former times, had become much more frequent since 1925. During the decade preceding 1925 approximately one to three cases of leukemia came under observation during one year in the clinic. After this date the number of leukemias admitted to the clinic rose to three to seven cases yearly. In addition to this absolute and (in the opinion of Curschmann) actual increase in the incidence of leukemias there occurred a remarkable shift in the type of leukemias observed. Since 1925, the acute variety of leukemia, formerly extraordinarily rare, became relatively common, representing more than 33 per cent of the total number of cases (eighty one) studied from 1925 to 1930. While Curschmann's analysis of the cases did not reveal any relation of this increase to some type of exogenous or endogenous factor (occupation, trauma, infection, tuberculosis, syphilis, malaria, and septicemia), there still remains, as the most probable explanation of this phenomenon, the supposition that some new undetermined exogenous factor or factors have been active in late years. It is less likely that the biological condition of the patient population of the clinic should have changed in such a radical fashion. This conclusion is supported by the fact, that during the same period a similarly spectacular increase of other blood dyscrasias, especially of the agranulocytic and aplastic anemic varieties, has taken place, which could be traced to certain types of aromatic compounds.

B. OCCUPATIONAL LEUKOBLASTOSES AND LEUKOBLASTOMAS

The various agents of occupational nature, which have been related etiologically to the occurrence of leukemoid, leukemic, and leukoblastomatous reactions, may be divided into two main groups, namely, those of more or less well-defined chemical (benzol, tar, and crude mineral oil) or physical (roentgen-rays and radioactive substances) character and those of nonspecific, mechanical-traumatic or traumatic-infectious type.

a. Chemical Agents

1. BENZOL

Chemical and Technological Aspects. Benzene, a cyclic hydrocarbon of the formula C_6H_6, is a distillation product of tar and is the principal constituent of an impure commercial product marketed, also, under the name of benzol. This substance is a colorless liquid having a characteristic odor and taste. While readily miscible with many other organic solvents, such as ether and alcohol, it is relatively insoluble in water. It should not be confused with a similarly named substance, benzine, which is a distillation product of petroleum and used for many purposes for which benzol is employed. Benzine consists of a mixture of non-aromatic hydrocarbons having the formula C_6H_{14} and C_7H_{16}.

The great importance of benzol as an occupational health hazard comes from its extensive use in many industrial operations and its use as a constituent of numerous industrial products (Rep. Internat. Lab. Office; Selling and Osgood; Holstein; McCord; Schilling; Greenburg, Mayers, Goldwater and Smith; and Bowditch and Elkins). Benzol and its derivatives play an important part in the manufacture of explosives, dyes, drugs, aromatic chemicals, lacquers, paints, paint removers, bronzing, silvering and gilding liquids, rubber cements, artificial leather, natural leather enamels, waterproof fabrics, and storage batteries. It is widely employed as a solvent of rubber, resins, fats, oils, and alkaloids, and therefore is used in cleaning machinery, dry cleaning clothes, decorating pottery, electroplating, lithography, photography, and many other industrial processes.

Toxicological Aspects. The notoriety of benzol as an industrial health hazard is principally derived from its injurious effect upon the nervous tissues (causing narcosis, lowering of body temperature, and impairment of oxidative metabolism) and upon the cells of the blood and hematopoietic organs (erythrolysis, hemorrhagic diathesis, and degeneration of the erythropoietic, myelopoietic, and ultimately lymphopoietic tissues causing leukopenia and aplastic anemia) (Weil; and Feller). These tissues develop an increasing sensitivity with repeated exposures to the toxic action of benzol (Intern. Lab. Office). This observation has been confirmed experimentally in animals by Pugliese, who reported that animals became, upon repeated exposure to benzol, intolerant to doses to which they had been previously resistant.

Leucocytotic, Leukemoid and Leukemic Reactions. Numerous observations suggest that the action of benzol upon the hematopoietic tissue is not always of a degenerative and hypoplastic nature, but that it may elicit an initial transitory or even prolonged hyperplastic, leukopoietic response. Thus, a transitory leucocytosis frequently represents the primary reaction of a benzol poisoning that results in a leukopenia (Selling and Osgood; and Intern. Lab. Office). Even the presence of a leukopenic, anemic and purpuric state, caused by benzol poisoning, may be associated with a marked myeloid hyperplasia

of the marrow and the presence of heterotopic myeloid foci in the spleen and liver (agnogenic myeloid hyperplasia) (Weil; Gall; Anderson; Cabot; Martland; Hamilton; Erf and Rhoads; Hunter; Mallory, Gall and Brickley; Rawson and Parker; and Jackson).

In animals similar observations have been made repeatedly in connection with benzol poisoning of mild and prolonged types. The development of a leucocytosis with hyperplasia of the bone marrow, associated with a moderate anemia, was seen by Schillowa in rabbits which received subcutaneous injections of benzol (0.1 to 0.05 cc. per kilo for 11 to 15 months). From the results obtained with the experimental inhalation of benzol fumes, Paul, Friedlaender and McCord concluded that benzol in low concentration may exert a stimulating effect upon the blood-forming tissues, especially the erythroblastic component. Similar effects were obtained by Schmidtmann, who exposed animals to benzol fumes in low concentration for a period of two hours, three times a week. The marked leucocytosis obtained persisted for some time, was followed by leukopenia, and ultimately by anemia. There were heterotopic, metaplastic, myeloid proliferations in the spleen during the early stage of exposure, while in the later stages fibrosis and hemosiderosis developed.

These leucocytotic reactions of the blood and the reported hyperplastic manifestations in the bone marrow, frequently associated with leukemoid heterotopic myeloid foci, which were observed in several cases of occupational chronic benzol poisoning in human beings and animals (experimentally produced conditions), are of immediate significance in connection with the occurrence of leukemia resulting from a prolonged occupational exposure to benzol fumes (Hamilton-Paterson).

Two cases of chronic benzol poisoning, showing a myelogenous leukemic blood picture, were mentioned briefly by Hamilton, who stated that a third similar case had been observed by Martland. The absence of any detailed data regarding exposure and associated symptoms greatly impairs the value of this evidence.

Delore and Borgomano reported a case of chronic benzol poisoning in detail. An acute myeloid leukemia developed in a chemist, 41 years old. This individual had been exposed to benzol fumes for five years, when engaged in the manufacture of pyramidon (containing aminopyrine). The blood examination showed 532,000 leucocytes with 80 per cent myeloblasts, 8.0 per cent neutrophilic myelocytes, 2.0 per cent eosinophilic myelocytes, 1.0 per cent basophilic myelocytes, 6.0 per cent polymorphonucleated leucocytes, and 3.0 per cent lymphocytes. A colleague employed in the same room and exposed to the same agent died from aplastic anemia, an incident which was of essential assistance in the interpretation of the etiologic relations existing in both blood dyscrasias. A second case of myeloid leukemia of allegedly benzolic origin was cited by Weil. This individual, a 62 year old man, was employed in a rubber factory where he came into contact with benzol fumes. He was

jaundiced, anemic, and had 25,900 leucocytes, 98.0 per cent of which were of myeloid origin. At autopsy the spleen and bone marrow showed morphologic lesions characteristic of an immature myeloid leukemia.

While the individuals in the last two cases cited were exposed to relatively large concentrations of benzol fumes, Falconer reported a case of leukemia in an employee who inhaled comparatively small amounts of this substance in a can factory. This individual was employed in the transportation of can ends from a conveyor to the warehouse, and inhaled benzol fumes given off by a solution of rubber applied to the can rims. When the leukemic worker was first seen he had 8,100 leucocytes (32.0 per cent lymphocytes, 62.0 per cent neutrophiles, and 6.0 per cent monocytes), 1,530,000 erythrocytes, 50.0 per cent hemoglobin, and 62,000 platelets. After one year, following a course of treatment consisting of blood transfusions, administration of sodium cacodylate, and Blaud's pills, he improved enough to return to work. Upon subsequent examination two years later, this individual had 13,200 leucocytes (36.0 per cent neutrophilic leucocytes, 56.0 per cent lymphocytes, 6.0 per cent monocytes, and 1.0 per cent eosinophilic leucocytes). From this period on there was a gradual and consistent rise in the number of leucocytes during the next two years, ultimately reaching 140,000 cells (98.0 per cent lymphocytes and 2.0 per cent neutrophilic leucocytes). The platelets had decreased to 34,000. At autopsy there were lymphatic leukemic lesions in the bone marrow, liver, spleen, and kidney. An actual benzol hazard existed as attested by the occurrence of four additional cases of benzol poisoning among employees of this plant.

In the analysis of this case, Falconer mentioned that the treatment with arsenicals might have depressed the myeloid tissue and simultaneously stimulated the lymphopoiesis, thereby introducing a complicating etiologic factor. He felt that the evidence available, while not definitely proving the etiologic interrelation between the exposure to benzol and the development of the lymphatic leukemia, made such a connection probable, especially as there occurred a gradual transition from changes typical for chronic benzol poisoning into those characteristic for lymphatic leukemia. This latter reaction was interpreted by him as the result of an overcompensatory measure of the lymphatic tissue.

A second case of chronic lymphatic leukemia in an individual exposed to benzol fumes for a period of ten years in a rubber factory was reported by Tareev. The leukemia reacted favorably to benzol medication but was refractory to roentgen-rays and Fowler's solution. A more recent addition to this list of leukemias, following an occupational contact with benzol, was recorded by Sabrazes and Bideau. These investigators observed a myelogenous leukemia in a machinery oiler (20 years old), who used a lubricant containing benzol. The hands and face of this individual were constantly covered with the oil during working hours over a three year period. In asserting the exist-

ence of a causative correlation between occupational exposure to benzol and myelogenous leukemia, the authors pointed out that nearly all commercial lubricating oils contain traces of benzol, especially the heavy types of oils. A case of acute aleukemic leukemia following exposure to benzol fumes was recorded by Thompson, Richter and Edsall in 1934. Perrin, Kissel and Pierquin reported recently a case of acute benzol leucosis, while Pessati and Vigliani were able, in 1938, to collect 10 cases of benzol leukemia from the literature (8 in males and 2 in females).

American investigators, studying workers employed in several artificial leather factories, shoe manufacturing plants, and fast-press rotogravure printing plants in the New England States and New York City, added three new cases of benzol leukemia, apart from several cases with leucocytoses and leukemoid reactions. A myeloid leukemia was found in a man, 38 years old, exposed for several years to the inhalation of benzol fumes in a rotogravure printing establishment (Erf and Rhoads). Two cases of myelogenous leukemia, one acute and the second chronic, were observed by Hunter; and Mallory, Gall, and Brickley, following prolonged exposure to benzol fumes in low concentrations. The latter investigators studied a case of acute, aleukemic, lymphoblastic leukemia masquerading under the clinical picture of an aplastic anemia in a boy, who used to play in a painter's shop. Special attention may be called in this connection to an important observation made by Hunter. He found that the first hematological symptoms of a chronic benzol poisoning may become manifest long after exposure to this injurious agent has ceased. Langelez noted from his experience with chronic occupational benzol poisoning in Belgium, that not only cases of atypical aplastic anemia with hypertrophy and myeloid metaplasia of the leukemic type are observed, but also acute and chronic leukemias.

Etiological Aspects. Teleky agreed with Falconer, in that a special individual susceptibility and potential leukemic reactivity must be present, if exposure to benzol and subsequent benzol poisoning are to lead to the development of a leukemia. This opinion is shared by Schultz, who conceded that under these conditions the claim of causative interrelations between exposure to benzol and leukemia may be granted. This conception was rejected by Schmidtmann who considered such occupational factors as purely coincidental. Schmidtmann pointed out that the transition of a leucocytosis, resulting from an occupational benzol hazard, into a leukemia has not been observed, and that the so-called "leukemias" produced in animals after experimental exposure to benzol were nothing but irritation hyperleucocytoses. A similar scepticism as to the actual occurrence of benzol leukemias was voiced by Richter, who argued that leukemias usually appear spontaneously. Such reasoning has little weight, because a term like "spontaneous" represents, along with "idiopathic," "essential," or "primary," evidence of our ignorance in etiologic respects.

In view of this controversial situation, it is fortunate that some experimental studies exist which supply confirmatory evidence to the probability or actuality of an occupational origin of such blood dyscrasias. The development of leukemic (three) and aleukemic (five) conditions in eight out of fifty-four mice treated with small doses of benzol over an extended period of time was observed by Lignac. There were two lymphosarcomas, one lymphoblastic leukemia, one eosinophilic aleukemia, two basophilic aleukemias, and two myeloid aleukemias. Leukemic lesions were absent in 1,465 mice which were studied for other reasons. Lignac's conclusion, in regard to the existence of interrelations between treatment and leukemia, received some support by the metabolic studies of Hess, who noted that the marked increase in aerobic and anaerobic glycolysis and the impairment of respiration of liver sections from mice treated with benzol was suggestive of a leukemic disposition. The causative mechanism active in the production of the experimental leukemia is, according to Lignac, as follows: small doses of benzol cause a minor destructive effect upon the hematopoietic tissue; this is followed by a regenerative phase; and with continued repetition of these two reactions by prolonged treatment given at proper intervals, the proliferative stimulation may become exaggerated and result in a transformation of the hyperplastic reaction into a leukemic one.

The combined clinical and experimental evidence presented, concerning the causative interrelations between occupational exposure to benzol and the development of leukemia, seems to indicate that such a connection is not a mere possibility but a great probability, and even an actuality. There occurs evidently a marked variability in the individual susceptibility and reactivity to benzol. This fact may account, in part, for the different types of hematopoietic tissue responses to this substance. The dose, the duration of exposure, and the interval between the individual exposures are obviously of great significance.

Preventive, Precautionary, Technical, and Sanitary Aspects. From the evidence presented and the conclusions drawn, the indication for strict medical supervision of the large group of workers occupationally exposed to benzol is inescapable. This surveyance should be constant and unremitting, and should include periodic blood examinations for the presence of quantitative and qualitative changes of the various blood constituents. It may be advisable to examine the urine for the presence of ethereal sulfates of benzol, utilizing the Obermayer method for indican and determining the inorganic sulfur portion, according to the procedure of Schrenk, Yant and Sayers. These tests are of limited value, since they are not specific for benzol poisoning and may be influenced by various internal and external factors (Kammer, Isenberg and Berg).

The proposal of Hagen, who recommended an ample dietary supply of vitamin C for workers exposed to benzol, merits consideration. Resistance to the effects of benzol is strengthened by this vitamin, as benzol poisoning is

accompanied by the development of a vitamin C hypovitaminosis. A daily dose ranging from 75 to 400 mgm. of vitamin C is considered by Hagen as an adequate amount for therapeutic and prophylactic purposes.

The most effective means of combatting this occupational hazard is of a technical nature and consists of the complete elimination of benzol fumes from the atmosphere of the working environment. This aim may be achieved, in many instances, by the introduction of a closed system in the production. The installation of an efficient exhaust ventilation and a frequent periodic determination of the benzol concentration in the air of the workroom to detect leaks and defects may aid in achieving this goal. As the use of a closed system is not always practical, the replacement of benzol by the less toxic benzine or some other less harmful solvent should be considered and insisted upon.

At present, no country has officially recognized benzol leukemia as a compensable occupational disease. Several countries include aplastic anemia and related conditions caused by occupational exposure to benzol among this class of industrial disorders.

II. BENZOL DERIVATIVES AND OTHER AROMATIC COMPOUNDS

A great deal of experimental evidence exists incriminating various benzol derivatives and other aromatic compounds in the production of leukemoid and leukemic conditions. Phenylhydrazine and its derivatives have been proved repeatedly as the cause of extensive, heterotopic, myeloid proliferations in the liver, spleen, kidney, and lymph nodes and of hyperleucocytoses of leukemoid character (Jaffé; Seitz; Itami; Bratley; Hueper; v. Domarus; Long; Lüdke; Pappenheim; and Heck and Hall). Similar organic changes were observed after the administration of chemically related hemotoxins, such as saponin and pyrogallol.

Small amounts of indol, which is known for its anemiogenic and leukopenogenic properties (Büngeler), was repeatedly injected into experimental mice. Leukemia developed in seventeen of the ninety-seven animals surviving for more than eight months. An aleukemic, lymphatic leukemia was observed in three mice; one had a lymphosarcomatosis, four exhibited a myeloid leukemia, and nine showed an aleukemic, myeloid leukemia. A diversity of leukemic responses were exhibited similar to those observed in occupational benzol leukemias. The incidence of the leukemic reactions, among the mice so treated, increased with the duration of the treatment. The organs of these animals revealed an elevated glycolytic activity and the leukemic reactions followed a preliminary stage of anemia and leukopenia.

Recent investigations with different synthetic, carcinogenic aromatic hydrocarbons and tar have shown that these more distant relatives of benzol possess carcinogenic properties and may elicit leukemoid and leukemic responses. The occurrence of leukemia in 2 mice and lymphosarcoma in 1 mouse, out of 60 mice repeatedly injected with water soluble 1.2.5.6-dibenzanthracene-9.10-

endo-alpha-beta-succinate, was reported by Burrows and Cook. In addition to the leukemia two of the mice exhibited a sarcoma. From these observations the authors drew the tentative conclusion that an etiological interrelation existed between the treatment given and the leukemia which developed afterwards.

This connection is more doubtful in an observation reported by Parsons, who injected the same compound into mice and obtained a spindle-cell sarcoma as a primary response. When this sarcoma was transplanted into other mice a typical myeloid leukemia developed instead of a sarcomatosis. A similar observation was made by Lewis after a transplanting of two sarcomas produced in mice by the injection of 1.2.5.6-dibenzanthracene. The animals receiving the implantation developed a myeloid metaplasia of the spleen and a marked leucocytosis. The causative mechanism of this unusual phenomenon may be twofold. The transplanted tissue of the primary tumor still contained some of the injected hydrocarbon, causing the leukemoid or leukemic reactions, respectively (the presence of the hydrocarbon was demonstrated by Berenblum in several successive transplants); or, the introduction of the transplanted neoplastic tissue elicited in the host a hyperplastic response from the hematopoietic tissue (this has been observed frequently in mice after transplantation of neoplastic tissue and with the development of experimental and spontaneous tumors). Subsequent experiments conducted by Parsons with the same compound (1.2.5.6-dibenzanthracene-9-10-endo-alpha-beta-succinate) suggested that the first-mentioned possibility was probably the correct one. The subcutaneous injection of this chemical into mice for a period of 158 to 272 days was followed by the development of sarcoma in some and leukemia in others (26,000 to 160,000 leucocytes with myeloblasts, irritation forms, and Türk's and Rieder's varieties in small numbers). There was a change of the leucocytic-lymphocytic ratio from 1:2 (normal) to 10:1 (leukemic). The leukemic transformation of the blood was preceded by a marked rise of the eosinophilic leucocytes, which later on decreased again in number reaching subnormal proportions. A similar transitory eosinophilia was observed prior to the sarcoma formation. Similar observations were made by Perry and Ginzton, who found in many of a larger number of mice treated with 1.2.5.6-dibenzanthracene, general lymphomatosis and sometimes mononuclear infiltrations of the liver and kidney, suggestive of leukemia.

A myeloid transformation of the spleen and liver, in addition to the local formation of a carcinoma, was found by Beltrami and Bisceglie in mice painted or subcutaneously injected with 3.4-benzpyrene. The latter reported that a myeloid transformation of the liver and spleen and an activation of the reticuloendothelial cells of these organs and the histiocytes in the lungs occurred in rats injected with 1.2-antipyrine benzoate, which caused sarcomas at the site of application.

An atypical leukemia resulted from the intrasplenic injection of 3.4-benz-

pyrene into a mouse, according to Barnes and Furth. In subsequent studies with intrasplenic injections of 3.4-benzpyrene in a larger series of mice, Furth and Furth observed the development of a condition similar to a monocytic leukemia in 9 per cent of the animals treated. Eleven months after the injection of 3.4-benzpyrene (1 mg. in a one per cent solution of olive oil), repeated eight times, twelve out of seventy-five rats surviving for such a period exhibited a leucocytosis ranging from 27,000 to 165,000 cells; 79 to 93 per cent of these cells being neutrophilic (2.0 per cent myelocytes and myeloblasts, and 1-3 per cent hemocytoblasts) (Storti and Storti). The bone marrow showed myeloid hyperplasia, the spleen was enlarged and transformed into a myelogenous organ, while the liver did not contain any metaplastic myeloid foci.

The subcutaneous injection of 3.4-benzpyrene into five chickens by Oberling, Sannié, and Guérin resulted in a minor erythroblastic reaction in one animal and an erythro-myeloblastic leukosis in a second animal, while the others died without a hematic reaction of any kind. Lanza observed leukemia in rats after benzpyrene was injected into the bone marrow. Barnes and Furth reported the development of an atypical leukemia in mice following the intrasplenic injection of crystalline 3.4-benzpyrene. Law and Lewisohn observed a much earlier appearance of a general lymphomatosis in mice, which normally developed this condition at old age, after cutaneous applications of 9:10-dimethyl—1:2-dibenzanthracene.

A similarly interesting and important contribution to the leukemiogenic action of carcinogenic chemicals was made by Morton and Mider. These investigators painted methylcholanthrene, dissolved in benzol, on the skin of mice having a known genetic constitution. The substance was applied to different areas in alternation to decrease the chances of a cutaneous neoplastic response and to enhance the opportunity of observing primarily the systemic effects. Of 48 mice thus treated, 10 developed a hyperleucocytosis of leukemic proportions (90,000 to 139,000 cells) with corresponding lymphatic leukemic lesions in the lymph nodes, liver, spleen, skin, lung, bladder, kidney, and skeletal muscle.

Following the intraperitoneal injection of fifty white mice with a concentrated solution of impure 1.2-aminonaphthol in olive oil (a substance suspected as one of the causative agents of bladder cancer in dye workers), three cases of retotheliosis and one case of myeloid leukemia were found in thirty-six animals histologically studied (Hueper). The incidence of a "spontaneous" leukemia among this stock was relatively low (3-4 cases in about 1,000 mice examined).

There exists some experimental evidence supporting the contention that tar may possess leukemiogenic qualities. One out of twenty mice, injected with tar in the inguinal region by Lund, developed at this site a tumor diagnosed as an endothelioma, but which grew in transplants as a lymphosarcoma. Lignac

reported the occurrence of a lymphatic leukemia in one mouse and myeloid leukemia in a second out of a total of fifty-six subjected to repeated cutaneous applications of a tar and benzol mixture. The observations of Bernard and Laplane upon rats which had received injections of tar into the femur bone marrow are of equally doubtful significance. In one experiment they obtained persistent leukocyte increases up to 100,000 cells, usually accompanied by erythrocytes up to 14,000,000 cells. The reactions, in several instances, were purely myeloid in nature, while in others, of the erythro-leukemic type. In these animals the viscera did not contain any myeloid foci, indicating that the blood reaction was purely the result of an excessive bone marrow stimulation. Thomsen and Engelbreth-Holm injected tar into the bone marrow of sixty-two chickens every five days for two to three months, and found in nine fowls a myeloid hyperplasia of the marrow and a blood picture resembling that of a myeloid leukemia. Among nine tumors (sarcomas) of different types, obtained in twenty-one chickens injected with tar, McIntosh observed one leucosarcoma. Brandt painted the ear of a rabbit for a period of over a year with a pitch tar dissolved in benzol. At death there was a diffuse neoplastic infiltration of all the internal organs by a very immature type of white blood cell, which he related to the retothelial cells or the stem cell. Brues and Marble observed the occurrence of leukemia in Bagg albino mice after prolonged painting with tar.

These numerous experimental observations suggest that aromatic substances other than benzol may play an etiologically important role in the development of leukemia in man.

b. Physical Agents

1. Roentgen-rays and radioactive substances

Hematological Reactions. Roentgen-rays and radioactive substances, which are sources of radiating energy, are well-known for their injurious action upon the blood and blood-forming tissues. They have been the cause of numerous cases of serious and often fatal leukopenia and aplastic anemia (Mottram; Koelsch; Laborde; Lavedan; Amundsen; deLaet; Kaplan and Rubenfeld; Goodfellow; Engelbreth-Holm; Reiter and Martland; and Brandt and Lange.

Clinical and experimental evidence accumulating during recent years indicate that these physical agents may produce leucocytotic, leukemoid, and leukemic reactions of the blood as well as hyperplastic and leukemic proliferations of the hematopoietic organs. The number of published articles on this subject, during the last fifteen years, indicate that these blood dyscrasias are becoming constantly more important as disease reactions after occupational exposure to roentgen-rays and radioactive substances. This development becomes more significant as the incidence of cancerous reactions, following prolonged occupational exposure to these types of radiating energy, has decreased

definitely. In commenting upon this trend in opposite directions, by these two manifestations of radiation injury, Brandt suggested that although the greatly improved elimination of the hazard of direct radiation has essentially removed the principal source of cancerous responses, the danger from scatter rays, which he incriminated as the cause of hematic reactions, has persisted to an appreciable degree. The production of these secondary rays cannot be easily prevented, and the contact with them cannot be entirely avoided.

Exposed Occupations. The use of roentgen-rays and radioactive substances has grown rapidly during the last two decades by their increasingly widespread application in the fields of medicine, science, industry, arts, and commerce. The development has greatly increased the number of individuals exposed to these agents in occupational endeavors. It is probable that the introduction of these active agents into various industrial and commercial establishments possessing no appreciable previous experience in this field, such as the medical profession has acquired and learned to appreciate by painful experiences, may even add to the existing hazard. This may be brought about by the lack of careful observation of essential and adequate precautionary measures in the installation and operation of such equipment.

Radiation hazard of this type exists for the following occupations and professions: Scientific personnel of physical, physico-chemical, and biological laboratories, and the medical personnel of diagnostic and therapeutic institutes of radiology in hospitals and clinics; physicists, chemists, engineers, and mechanics engaged in the manufacture and testing of roentgen-tubes and radioactive substances intended for medical and commercial purposes; engineers and mechanics employed in the installation and repair of roentgen-apparatus; miners of radioactive ores; workers handling and using radioactive substances for commercial purposes (painting of luminescent dials and gunnery equipment and the manufacture of gas mantles); personnel of roentgen-ray laboratories of the electric industry (testing of micas used in electrical equipment for the absence of metal particles and verification of electric units hidden beneath insulating material of large electric mountings); personnel of roentgen-laboratories of the aviation industry (examination of wood for flaws and defects used in airplane construction); personnel of roentgen-ray and radium laboratories of the metallurgic industry (testing of castings for flaws and crystalline structure, and examination of alloys and testing of heat, pressure, and other mechanical stresses on metal parts); personnel of roentgen-laboratories of the chemical industry [examination of the structure of fibrils (cellulose, rayon, rubber, and proteins), and the effect of dyeing, light, heat, and chemicals on fibrils; and the study of amorphous and colloidal matter, crystals, and resins]; personnel of roentgen-laboratories connected with the art and jewelry trade (differentiation between natural and cultured pearls; and establishment of the authenticity of paintings, documents and similar matter); and the personnel employed in shoe stores using roentgen-ray equip-

ment (Friesleben; Koelsch; Brandt; Evans; Stewart; and Laborde and Leclercq).

Leucocytotic, Leukemoid, and Leukemic Reactions. The occurrence of hyperplastic responses to a certain agent, suspected responsible for cancerous or equivalent cellular reactions, represents evidence of definitely suggestive value supporting the actual existence of the suspected interrelations. It is significant that occupational and experimental exposure to roentgen-rays and radioactive substances does not always result in the production of anemic and leukopenic conditions with atrophy of the hematopoietic tissues. It may be frequently followed by a leucocytosis of the blood and hyperplasia of the bone marrow.

The factors underlying these divergent reactions are not as yet clearly understood. The dosage and duration of exposure of these types of radiating energy play an important role in this respect. It is a well-established fact that degenerative and atrophic changes of the hematopoietic tissue are the invariable results of exposure to large amounts of these agents at one time, or to repeated moderate amounts received within relatively short intervals (Heineke). The reactive variations seem to occur when the exposure is very prolonged in duration and sustained by small doses. Individual differences in constitution and endocrine activity were held responsible by Antonio and Mirto for the discrepancies in the post-irradiative reactions of the blood. They claimed that a post-irradiative leucocytosis with neutrophilia is characteristic for a macrosplanchnic constitution, whereas a leukopenia with relative or absolute lymphocytosis is typical for a longilinear constitution. Other theories and conceptions have been advanced in attempted explanations of the post-irradiative leucocytoses. Bürger speculated that the rays cause the production of a substance in the skin which exerts a stimulating effect upon the bone marrow. From his study of the action of roentgen-rays upon the blood-forming cells, Isaacs concluded that this agent stimulates the proliferation of the immature cells and hastens the maturation of the more mature elements, thereby shortening their normal span of life.

Martland, in a study of a series of chronic poisonings with radioactive substances (radium and mesothorium), has furnished some striking evidence, that even a very prolonged exposure to these agents might be associated with a hyperplasia of the hematopoietic centers of the bone marrow. The hyperplasia may be an initial over-compensating response of the bone marrow to the excessive destruction of the erythrocytes and leucocytes. This condition might last for years, and is characterized by an increased production of erythrocytes and, possibly, by a leucocytosis. A remarkable feature of the bone marrow during this hyperplastic stage is the presence of a large number of eosinophilic leucocytes in addition to the marked increase in the very immature and primitive blood cells (hemocytoblasts) and megaloblasts. The eosinophilic proliferation of the marrow, observed in the cases of Martland, is not accompanied by an

increase in this type of cells in the circulating blood. Other authors reported the presence of an eosinophilia of the blood as a characteristic feature in workers professionally exposed to roentgen-rays and radioactive substances (Aubertin; and Goodfellow). Laborde and Leclercq stated that the blood of radiologists often shows an eosinophilia (in 30 per cent of the cases present, but not surpassing 7 to 8 per cent eosinophilic cells) with a polymorphonuclear leucocytosis, both being expressions of a hyperfunction of the bone marrow. Such a reaction may culminate occasionally in the development of a leukemia, which is of a myeloid type. Similar observations were recorded by Cornil and Rouslacroix, who made a hematological study of the personnel of the anticancer centers of Marseilles. They found that in addition to the existence of a hyperleucocytosis in some instances, there was an eosinophilia (6 to 10 per cent) in 23 per cent of the persons examined.

In a survey conducted by Stewart on the occurrence of industrial poisoning from radioactive substances (1929), this investigator found, among chemists employed in laboratories and plants handling this material, evidence of a bone marrow proliferation stimulating action following such an exposure. In four cases of radium poisoning, observed among workers of a plant in Connecticut, two had relatively high leucocytic values in the presence of a severe reduction of erythrocytes [1,970,000 erythrocytes and 10,200 leucocytes in the first case, and 768,000 erythrocytes and 18,000 leucocytes (40 per cent polymorphonuclears, 35 per cent large mononuclears, and 25 per cent lymphocytes) in the second case]. The appearance of an increased number of eosinophilic cells, indicating an overexposure, was occasionally accompanied by abnormal or embryonic leucocytes.

In addition to these relatively common leucocytotic, hyperplastic, hematic reactions after irradition with roentgen-rays and radioactive substances, a few cases were described in which the occupational exposure to these actinic agents resulted in the production of reactions of a strong leukemoid type. Preleukemic blood changes have been seen very rarely in radiologists, according to Laubry and Marchal, who mentioned that Aubertin observed two such cases. The radiation hyperleucocytosis lasted for several months after cessation of their professional contact with roentgen-rays; but 18 months later both men were again in good health. Such a quick return to normalcy was not always the outcome of leucocytic blood reactions of this genesis.

While engaged in a search for the occurrence of preparatory, subleukemic or preleukemic conditions in individuals exposed chronically to roentgen-rays, Aubertin made the following observations in a radiologist. This individual was a thirty-eight-year-old male, who had been in contact with roentgen-rays in his professional work for a period of thirteen years. This person suddenly developed an attack of extreme fatigue and his blood picture showed 5.27 million erythrocytes and 11,625 leucocytes, of which 63 per cent were polymorphonuclear neutrophiles, 6 per cent eosinophiles, 4 per cent

lymphocytes, and 27 per cent mononuclears. After a period of rest this radiologist continued his professional activities, and a year later suffered a second attack of severe fatigue accompanied by paleness. There were no skin or mucous membrane hemorrhages and no enlargement of the palpable lymph nodes. The blood examination revealed 4.66 million erythrocytes, 75 per cent hemoglobin; and 36,800 leucocytes, of which 75 per cent were polymorphonuclear neutrophiles, 2 per cent eosinophilic leucocytes, 1 per cent myelocytes, 6 per cent lymphocytes, and 16 per cent mononuclears. There were no nucleated erythrocytes observed. Because of these hematic changes the radiologist discontinued his work with roentgen-rays. In spite of this precaution a blood examination made two months later still showed 3.78 million erythrocytes, 80 per cent hemoglobin; and 31,000 leucocytes containing 70 per cent neutrophilic leucocytes, 7 per cent eosinophilic leucocytes, 5 per cent lymphocytes, and 18 per cent mononuclears. A slow amelioration of his blood condition occurred during the following year, at the end of which he had 3.98 million erythrocytes and 11,100 leucocytes, of which 54 per cent were neutrophilic leucocytes, 2 per cent eosinophilic leucocytes, 11 per cent lymphocytes, and 33 per cent mononuclear cells. The liver and lymph nodes were normal. A year later the blood still exhibited a leucocytosis of 20,700 cells with 54 per cent polymorphonuclear neutrophiles, 6.7 per cent eosinophiles, 0.3 per cent basophilic leucocytes, 1 per cent myelocytes, 7.3 per cent lymphocytes, and 31 per cent mononuclear cells. This case represented, in the opinion of Aubertin, a typical example of a hyperleucocytosis of considerable duration, caused unmistakably by a prolonged occupational exposure to roentgen-rays. In view of the absence of an appreciable number of immature leucocytes in the blood at any time during the observation period, Aubertin did not feel that the blood condition possessed a preleukemic character.

A second case of equal importance, supplementing and extending Aubertin's observations in the leukemic direction, was reported by Schilling. This report dealt with the blood dyscrasia exhibited by a thirty-eight year old radiologist, who had been active in roentgen practice for ten to twelve years. This individual had not observed the proper protective precautions and, because of this negligence, suffered atrophic changes of the fingers, friability of the nails, atrophy of the testes, weakness, emaciation and pallor. The blood examination showed 4.00 million erythrocytes, 80 per cent hemoglobin; 37,000 leucocytes; and a mononucleosis of 76 per cent. In spite of a course of arsenic treatments, the leucocytes remained low, the erythrocytes dropped to 2.10 million, the hemoglobin to 50 per cent, and neuralgic pains appeared. Several months later the patient had swollen lymph nodes in the neck and the spleen was just palpable. The urine contained albumin and leucocytic casts. A specimen obtained by puncture of a lymph node showed metaplastic myeloid hyperplasia. The leucocyte count showed 10,000 white cells with 14 per cent myeloblasts, 20 per cent promyelocytes, 4 per cent myelocytes, 1 per cent band-

shaped, neutrophilic leucocytes, 1 per cent segmented nucleated leucocytes, 55.4 per cent lymphocytes, 2 per cent mononuclears, 0.4 per cent basophiles, and 1.1 per cent atypical cells. The oxydase reaction was positive in all cells. However, the cells diagnosed as lymphocytes were probably oxydase negative myelocytes. The individual died with a diagnosis of micromyeloblastic leukemia. The autopsy revealed an atrophy of the spleen with a few scattered myeloid cells in the pulp, a liver without any myeloid infiltrations, which, on the other hand, existed in the kidney and chorioid plexus. The bone marrow contained many plasma cells, micromyeloblasts, promyelocytes and myelocytes, foam cells of plasma cell origin, and scanty erythroblasts. The clinical diagnosis of leukemia was modified on the basis of the post-mortem findings. This condition, a striking illustration of the great difficulties which may be encountered in the differentiation between a leukemia and a leukemoid reaction after occupational exposure to roentgen-rays, was interpreted as the result of a severe injury to the bone marrow with attempted myeloid repair and scanty myeloid heterotopic metaplasia.

It is fortunate that the observations made by Stewart on four chemists employed in studios in Pennsylvania and suffering from radium poisoning provide additional evidence, supporting the actinic origin of such conditions and showing the potential leukemic outcome of these reactions. Two of the four chemists developed, as the result of a long prolonged occupational exposure to radioactive substances, cutaneous malignancies, which in one case was complicated by a severe radiation anemia of a pernicious type. A third chemist displayed a blood disorder which exhibited at varying times a tendency to an anemic type or a leukemic variety. This individual was apparently in a transitional stage, in which the ultimate outcome of the hematic occupational injury was still in the balance. Such a final turn had been made in the fourth chemist belonging to this group. He was an individual, 39 years old, who had been exposed to radioactive material from 1912 to 1925, and who had been engaged in the manufacture of luminous dial paint until 1927. After having passed through a stage of leukopenia, he died from a myeloblastic leukemia.

The apparent rarity of such intermediary blood reactions is in sharp contrast to the considerable number of leukemias reported, for which causative relations were claimed concerning an occupational exposure to the actinic agents. There are, so far, twenty-one such cases on record, eighteen of which occurred in males and three in females (v. Jagič, Schwarz and v. Siebenrock; Carman and Miller; Davey and Whitby; Evans and Roberts; Weil and Lacassagne; Aubertin; Haagensen; Nielsen; Beclère; Loewy; Vaquez; Laubry and Marchal; Teleky; Weitz; and Stewart). The evidence offered in support of the alleged etiological connection with roentgen-rays and radioactive substances, respectively, is in a considerable number of these cases quite defective. In three of the four cases recorded by v. Jagič, Schwarz and v. Siebenrock, the

claim is based on mere hearsay. No detailed clinical data are available in regard to five cases mentioned by Aubertin and one case observed by Béclère. Post-mortem findings only are given in support of the case reported by Haagensen. Clinical and autoptic observations were made in only one case (Weil and Lacassagne), while extensive preleukemic blood studies, showing the gradual development of the hematic changes, were presented with the most recently recorded case of Weitz. In all the other cases the fully developed leukemia existed at the time of the first examination.

Exposure Time, Age, and Occupational Distribution. The great majority of persons affected were radiologists and assistants to medical radiological laboratories. The cases of three chemists engaged in research on radioactive substances were reported by Weil and Lacassagne; Loewy; and Teleky. The time of exposure varied from five to nineteen years, according to the data available in six cases. There was no reliable or even approximately accurate information existing as to the dose of radiating energy active in eliciting the leukemic response.

The age range was from thirty-four to fifty-three years. Additional preneoplastic or neoplastic reactions attributable to the professional hazard were noticed in two cases (radiodermatitis of the hand in Nielsen's case and carcinoma of the lung in the case of Loewy). Occupational exposure to roentgen-rays was blamed for the leukemia in fifteen instances, while professional contact with radioactive substances (radium, mesothorium, and thorium-x) existed in six cases (four chemists and two nurses in radium therapy departments). The leukemias observed were always of the chronic character, fifteen being of the myeloid type and six of the lymphatic type. The subjective symptoms, at the onset and during the course of these actinic leukemias, were identical essentially with those experienced in leukemia of cryptogenetic origin. There was an insidious beginning characterized by vague symptoms, such as fatigue, loss of energy, pallor, fullness in abdomen, and pain in the bones or substernal region. According to Aubertin, the duration of the disease is shorter than in the ordinary case. The average case lasts only eighteen months as compared to three to six years for the cryptogenetic variety (Weil; and Morawitz). It was emphasized by Weitz that the course of the disease in his case was relatively rapid, after the appearance of subjective symptoms. The total duration of the blood dyscrasia until death was six years, while the first appreciable subjective disturbances were noticed three years before death. Anemia was usually a late complication.

Diagnostic Aspects. There is little definite information available as to the primary hematic changes which may serve as warnings. The presence of an eosinophilia was mentioned by Aubertin as representing evidence of a certain hyperactivity of the bone marrow, disclosing a predisposition to leukemia. This change was strikingly present in the case reported by Weitz, whose patient showed, long before definitely leukemic changes were noted, a marked

eosinophilia (up to 20 per cent) which persisted into the leukemic stage. The frequent occurrence of a post-irradiation eosinophilia was already recorded, pointing in the same direction. Reference may be made to the observation by Parsons of a preleukemic, transitory eosinophilia in the blood of mice injected with 1.2.5.6-dibenzanthracene-9.10-endo-alpha-beta-succinate. The diagnostic importance of preleukemic basophilia (up to 10 per cent) was stressed by Weitz. The basophilia persisted during the leukemic stage and reached values of sixteen per cent. It can be anticipated that the introduction of routine, periodic blood examinations of the personnel of many roentgen-and radium-laboratories will prove to be of great value, by supplying more definite and extensive information in this respect. These examinations will be instrumental, also, in the discovery of additional cases of actinic leukemia as well as important intermediary and transitional stages between simple, regenerative, hyperplastic conditions and definitely leukemic manifestations.

Etiological Aspects. The much debated question as to the actual existence of etiological interrelations between this type of professional hazard, and the occurrence of leukemia has been answered differently at various times. The connection is purely coincidental or at least lacking sufficient proof, in the opinion of Schmidtmann, who referred in support of this contention to the absence of leukemia among miners of the Schneeberg district where radioactive ores are worked. The weight of this argument has been weakened greatly in recent times by the reports of Loewy and Teleky, concerning the occurrence of leukemia in two employees of the Joachimsthal establishment where an identical hazard exists. The probability of a causative interconnection was conceded by Selling and Osgood, who nevertheless felt that the number of cases observed was not sufficiently large to exclude coincidence. A similar opinion was expressed by Lambin; Rolleston; and Evans and Roberts. Laubry and Marchal contended that the radiating energy only produced a predisposition to leukemia, while another agent acted as the more important eliciting factor. The possibility that a secondary infection might play the role of this eliciting factor was considered by Weil. In a publication by Weil and Lacassagne, the opinion was expressed that the leukemia reported was the result of the provocative action of the rays of radioactive substances. This is based upon the fact that a coworker of the leukemic sufferer, who worked in the same room and was exposed about the same period to radioactive material, died from an aplastic anemia representing a recognized effect from the rays emitted. The leukemic patient showed an atrophy of the testes as evidence of his professional exposure to the rays. Weitz was equally positive that the leukemia in his patient was the direct result of the prolonged occupational contact with actinic energy. The supposition of a coincidental connection appeared unjustifiable to this author, in view of the many cases of leukemia reported among radiologists and employees of radiological laboratories. A similar opinion was expressed by Askanazy and Martland. A contradictory

conclusion recently advanced by von Spindler is based on insufficient information, and is supported by arguments of weak and dubious value.

A statistical approach to this problem was attempted by Nielsen, who realized clearly the dangers associated with such a procedure because of the small number of cases available for evaluation. According to Nielsen, the total yearly death rate from leukemia in Denmark was seventy deaths or 1 per 50,000 population. If this same ratio was applied to the roentgen-rays and radium workers the total number of individuals engaged in this work, for a period upward to ten years, would be 35,000. From such a calculation, the probability for a member of this profession to develop a leukemia of an occupational causation is incredibly high. Statistical investigations conducted by Levant on this aspect led to a similar result, that is, leukemia is 5 times more frequent among physicians practising radiology than among the medical profession in general.

The affirmative side of this question receives further support from the claims that the therapeutic administration of roentgen-rays or radioactive substances has been responsible for a myeloid leukemia in a woman (62 years of age) appearing after an intense and prolonged course of roentgen-ray treatments for uterine fibroids, as reported by Merkel, Wolf, and Nèel. A second case of this type was recorded recently by Rimbaud, Anselme-Martin, Lafon and Castagné. These investigators observed an acute leukemia in a man who had consumed, within a period of three weeks, a patent medicine containing radioactive material. The therapeutic administration of roentgen-rays to a tuberculous vertebra was in the opinion of Küttner, the cause for a myeloma in this bone. It must be admitted that the last two cases cited carry scarcely any convincing weight, as the data available are too scanty.

The acknowledgment of the existence of actinic leukemias meets with additional difficulties through the occurrence of the myeloid and the lymphatic forms of leukemia. The greater susceptibility of the cells of the myeloid series to radiating energy, and the occurrence of post-irradiative myeloid hyperleucocytoses as the result of an actinic stimulation of the myeloid tissue make the development of a myeloid leukemia a plausible possibility. The existence of lympatic leukemias as the result of the same agent appears to be less readily conceivable. In view of the undoubted production of an aplastic anemia by the action of roentgen-rays, it was not surprising that the production of a myelogenous leukemia should be reported, wrote Farley; but the production of a lymphatic leukemia by such means should not be credited without a very close scrutiny.

Some important arguments can be advanced in an attempt to explain the possibility of such alternative lymphoid reactions. An absolute lymphocytosis or mononucleosis in the presence of an unchanged total number of leucocytes is the most frequently observed hematic reaction of roentgen-ray workers (Lavedan; Mottram; and Nielsen). The increase of the mononuclear cells

may attain such proportions that there is an inversion of the normal leucocytic-mononuclear ratio. It may, also, be argued, that since the lymphoid elements are apparently less sensitive to the rays than the myeloid cells, the lymphoid cells might respond with a more marked and ready regenerative proliferation than the more severely injured myeloid cells. Consequently, Amundsen has maintained that the lymphatic leukemia of roentgen-ray workers should be regarded as a lymphocytic regeneration overshooting its mark. The correlation hypothesis of Ziegler, recently propounded by Wiseman, Doan, and Erf, provides an additional conception through which the occurrence of lymphatic leukemias may be explained. The primary destruction of the myeloid tissue by radiating energy would cause, according to this theory, a serious disturbance in the leucocytic-lymphocytic equilibrium, resulting in a release of the lymphoid elements from the growth restraint of the myeloid parts. The data and considerations given above represent important circumstantial evidence, but are lacking in definitely convincing value, unless supported by experimental observations confirming the clinical findings. Experimental studies conducted by several investigators particularly during recent years supply the confirmatory evidence.

Experimental Roentgen- and Radium-Leukemia. The early experimental work of Ziegler; Heineke; and Fischer-Wasels had already shown that mice exposed to small doses of roentgen-rays developed a myeloid transformation of the spleen, and a myeloid hyperplasia of the bone marrow. The appearance of large histiocytic infiltrations in the organs of white mice after the administration of small amounts of roentgen-rays was reported by Calò. The formation of extramedullary, regenerative, hematopoietic foci, and the appearance of myeloblasts, myelocytes, lymphoblasts, plasma cells, and megakaryocytes in the circulating blood were noted by Jin following repeated intravenous injections of a colloidal thorium-X solution into rabbits. The radioactive thorium-X particles were stored in the reticulo-endothelial cells of the spleen, liver, and especially the bone marrow. Mello recorded the development of a leucocytosis after a single irradiation with roentgen-rays. The intravenous injection of thorium-X caused a hyperplasia of the bone marrow in the presence of a leukopenia in the circulating blood. An excessive regenerative proliferation of the bone marrow was observed by Lacassagne, Lattès, and Lavedan in rabbits which had received small doses of polonium intravenously (polonium emits only alpha-rays).

In addition to these hyperplastic responses of the hematopoietic tissue to exposure to small doses of radiating energy, there exists experimental evidence attesting to the possibility of leukemic reactions under such conditions. A marked rise in the incidence of leukemia among mice irradiated with roentgen-rays to increase their susceptibility to lymphosarcomatous transplants was reported by Krebs, Rask-Nielsen, and Wagner. The frequency of leukemia among these mice rose from 0.058 per cent (normal) to 3.6 per cent after

irradiation. Irradiated, non-leukemic mice showed a myeloid hyperplasia of the bone marrow and spleen. These investigators concluded that the increased incidence of leucoses might be the result of the treatment with roentgen-rays. A marked rise in the number of lymphoid and myeloid leukemias (from 19 per cent normally to 74 per cent) among female mice with spontaneous mammary carcinomas following repeated, total irradiation with small individual doses (30 to 80r) of roentgen-rays was reported by Hueper. This result was attributed to the activating effect which the roentgen-rays exerted upon an inherited predisposition to leukemia present in the strain of mice used. Using mice of the same strain as used by Hueper, Furth and Furth succeeded in increasing the myeloid leukemia incidence eightfold and mediastinal lymphomatosis sevenfold by the repeated exposure of young animals to roentgen-rays (200 to 400r). These authors mentioned that the leukemic responses appeared in the irradiated mice at an earlier period than among normal, untreated animals. They maintained that the higher incidence of leukemias must be attributed to the roentgen-rays administered. The development of a reticular cell sarcoma of the bone (Ewing's tumor) was observed by Schürch and Uehlinger in a rabbit 36 months after the implantation of 5 mcg. of mesothorium in vaseline into the femur. Other rabbits equally treated showed osteogenic sarcomas.

Medico-Legal Aspects. The critical analysis of the combined clinical and experimental evidence leaves little doubt that the occupational exposure to roentgen-rays or radioactive substances may play an important causative role in the development of both myeloid and lymphoid leukemic manifestations. At the same time other conditions, such as the dose, length of the interval between different exposures, duration of exposure, and constitutional reactivity of the exposed individual, are of importance in determining the type of resulting hematic reaction—whether it is aplastic, dysplastic, hyperplastic, or neoplastic in character.

The demonstration of radioactivity of the organs was considered by Schilling as an essential requirement for the recognition of a leukemia of radioactive origin. Schilling conceded that this condition could be fulfilled only if the introduction of the radioactive matter into the organism was of relatively recent date. He added, that in the presence of a long interval between exposure and examination for organic radioactivity the body would have had time to eliminate the causative matter. This conception is contrary to existing observations in radium poisoning. There is only one case on record in which an attempt was made to demonstrate the radioactive agent in the organs (Weil), and the tests made (photographic method) were negative in this case. While positive evidence in this respect may be looked upon as helpful in proving the actinic origin of a leukemia, it should not be regarded as absolutely essential, since leukemias related to the exposure to roentgen-rays would not be amenable to a test of this type.

The recognition of an actinic leukemia must be based primarily upon the proper historical data in regard to an occupational exposure to roentgen-rays or radioactive substances, and, whenever possible, upon blood examinations made before the leukemic condition became manifest, demonstrating preleukemic changes. Occupational actinic leukemias have not been, so far, officially recognized in any country except France (International Labour Conference) as a compensable occupational disease; but the aplastic hematic conditions caused by roentgen-rays and radioactive substances have been listed in this group in several countries.

II. TRAUMA

Leukemia. Several exogenous agents, exerting an ill-defined and complex effect upon the organism and often related to occupational activity, have been incriminated in the causation of the various leukemic and neoplastic conditions of the hematopoietic tissue. Mechanical trauma with its sequelae, such as hemorrhage, concussion of the tissues with cellular dislocation and disturbance of intercellular connections, generalized circulatory disorders caused by shock, as well as secondary infections, represent the most frequently cited agents in this respect (Stempel; Diez; Bousser; Hirschfeld; Thiem; Schilling; Isaac; Morawitz; and Ebstein). Purely psychic trauma has been associated rarely with these hematic responses, while primary infections of the acute type (septicemia) and chronic character (nonspecific bacterial infection, tuberculosis, and malaria) figure prominently in the various etiologic claims advanced in regard to leukemia, myeloma, and lymphosarcomatosis (Ewing; Sternberg; Cherry; and Hueper).

Leukemia (Psychic Trauma and Mechanical Trauma). The contention that trauma may play a causative role in the production of a leukemia is almost as old as the knowledge of the disease itself. The first case of so called "traumatic leukemia" was reported by Virchow (1853), who established the histological concept and term of leukemia. Since then many additional cases have been recorded (Helly; Koelsch; Stern; and Bousser). Stern collected sixty cases of traumatic leukemia from the literature, Bousser recently reviewed a series of thirty-eight cases, and Olovson reported on sixty-nine cases. The total number of hematic dyscrasias and neoplasms of alleged traumatic origin, so far reported, is approximately between eighty to ninety. In addition to these manifestations in man, there are a limited number of reports dealing with the occurrence of a traumatic leukemia in animals: dogs, horses, and cattle (Jarmai; Wirth; and Weber).

While the absolute number of traumatic leukemias and related disorders is not remarkable, this fact does not detract from their distinct scientific, practical, and particularly medico-legal importance. These maladies will gain greater significance and interest in view of the present rapidly increasing knowledge concerning the etiology of blood diseases in general. Their im-

portance will be weighted further as a result of the introduction and elaboration of workmen's compensation laws in a constantly growing number of states.

Psychic trauma such as shock and sudden fright was mentioned by Ebstein as a possible cause of a subsequently developing leukemia. However, according to our knowledge of proliferative processes, an isolated and transitory psychic upset cannot represent the direct and main cause of a leukemia under any ordinary circumstances. Interrelations between the function of certain parts of the central nervous system and the leukopoietic activity are at present not established reliably and are mainly speculative. Any serious theoretical consideration of such a possibility would require the development of some unusual complications, such as more or less persistent metabolic or endocrine disturbances resulting from a psychic injury. These in turn might actuate the subsequent production of the leukemia (Lambin; Engelbreth-Holm; and Naegeli). As such organic sequelae following a psychic trauma are likely to occur only in predisposed individuals, the trauma would play at best a secondary precipitating role under markedly unusual conditions. None of the reported cases of leukemia after psychic trauma was preceded or followed by generalized metabolic or endocrine disturbances. Psychic trauma has not resulted as yet in the development of a leukemic condition.

Mechanical trauma may be the result of a blow sustained during occupational activity (struck by a pole, rod, bar, or tool), a contusion sustained by a crushing injury (hit by falling tree or being run over by wagon or automobile), a concussion brought about by a fall from a great height, a laceration produced by a fall against a sharp pointed or edged instrument (a piece of machinery or furniture), or by gunshot. The injuries resulting in disturbances of the tissue relations, hemorrhages, edema, and inflammation and allegedly followed by, or related to, a leukemia may be classified as follows:

Direct or indirect trauma to

a. the spleen or splenic region
   (Koschin; Pansini; deChapelle; Gowers; Herrmann; Olovson; Knoth; Kutschera; Morax; Ponfick; Keller; Klemperer; Wallace and Robertson; Thomsen; and Reckzeh);
b. the bones, especially the long bones and vertebrae particularly in the form of a local or general concussion of the bony structures
   (Schimert; Rösler; Olshausen; Norrikoff; Lévai; Görtz; Kutschera; Liniger; Neumann; Stempel; Kaufmann; and Olovson);
c. some other organ; sometimes associated with a single large or prolonged small hemorrhages, at other times consisting only in simple physical overexertion, strain, a jerk, or exposure to cold
   (Bauer; Reckzeh; Böttcher; Greiwe; Wittgenstein; Herrmann; Koopmann; Koschin; Kutschera; Martinelli; Bousser; and Lüder);
d. some organ, followed by an acute or chronic infection
   (Steinhaus; Hirschfeld; Curschmann; and Kaufmann); or

e. the same region or organ at several occasions

(Thomsen; Rösler; Keller; Schimert; Morax; and Kaufmann).

The etiological significance of the above listed types of trauma in their relation to leukemia is a highly controversial matter. The existence of a causative interconnection between trauma and leukemia is considered possible by Lévai. Schilling remarked that the term "traumatic leukemia" is insecure scientifically, and recommended that allegations made to the traumatic origin of a leukemia should not be recognized during the present state of knowledge. He did concede the possibility of an aggravation of a preexisting leukemia or the precipitation of a silent leukemia into a manifest state by a trauma. The traumatic genesis of a leukemia should be acknowledged, in the opinion of Isaac, if no evidence exists that the leukemia was present at the time of the accident, and particularly when the leukemia becomes apparent within a few weeks to several months following an accident involving the spleen or long bones. While believing that there is no constant relationship between trauma and leukemia, Ebstein is convinced that leukemia may follow a trauma which causes a concussion of the entire body, the bone marrow, or involves the spleen. Thomsen and Engelbreth-Holm cited Lange as contending that leukemia usually follows a mechanical trauma. Krumbhaar conceded the possibility that certain traumatic episodes, such as colds, chills, back injuries, and infections, may be the fundamental or, at least, the precipitating cause of a myelogenous leukemia. In the latter case the leukemic condition was dormant at the time of injury, and had been forming for an indefinite period previously. A causative connection was considered as uncertain by Morawitz and Deneke, who did admit that it could not be denied definitely, especially when the trauma involved the spleen or the long bones and a sufficient interval elapsed between the trauma and the onset of the leukemic symptoms. Even under such circumstances the assumption of a causative relationship remains only a probable one. Moreover, these authors did not believe that a traumatic infection may elicit an acute leukemic response, as many investigators contend. Desjardins favored the conception, that a chronic infection may play a causative role in the production of lymphosarcoma and occasionally leukemia, provided a predisposition of some sort exists which supplies a suitable background for the immediate cause.

A definitely negative attitude upon this question was taken by other authors. Trauma was considered by Hirschfeld as merely an aggravating factor acting upon a preexisting leukemia. A similar opinion was expressed by Diez, who cited Martelle in support of his conception. Stern looked upon the existence of a traumatic leukemia with great scepticism. After a detailed analysis of the data of thirty-eight cases studied by him, Bousser came to the conclusion that the relationship between trauma and leukemia is still obscure. The present attitude of several German experts (Kaufmann; Schilling; Stern; Hirschfeld; and Isaac), according to Boucher, may be summarized as follows: in

the majority of traumatic leukemias reported, the trauma simply revealed a preexisting leukemic condition; in some of the remaining cases, the trauma may have aggravated such a state; the present data do not support the actual occurrence of a traumatic leukemia; and the responsibility of an accident for the development of a leukemia should be acknowledged if the circumstantial evidence leaves any doubt as to the actual existence of such an interrelation, as the possibility of such connections cannot be absolutely and definitely denied. This consideration is particularly applicable, if the trauma is produced mechanically and not psychically and if the leukemia is myeloid and not lymphoid in nature, since the latter variety has rarely been mentioned as a sequela of a trauma. Stempel regarding the fulfillment of the following conditions as adequate evidence of a traumatic origin of a leukemia: the trauma must involve the spleen; the injured individual must have been healthy and well before the accident; the leukemia must become manifest within one year after the trauma; and a relatively normal period must intervene between the trauma and the appearance of the first leukemic symptoms.

An analysis of the histories of the traumatic leukemias reported leads to the conclusion that a certain number of these cases must be excluded because of inadequate clinical and especially hematological evidence offered in support of the leukemic diagnosis (Mosler; Gowers; Ebstein; Lüders; Graziani; Klemperer; Tabora; and Stefanelli). The interval elapsing between the trauma and the leukemia is too long, in other cases (five years), to make any connection between the two events in any way likely or deserving of any serious consideration (Ebstein). In an appreciable number of the case records, data are not available as to the health status before the accident, the length of time between the accident and the first leukemic symptoms, or the type of symptoms existing during this interval. The presence of such serious defects in the evidence makes a reliable evaluation difficult or impossible in the individual case. A blood examination has not been made in a single case during a reasonably short time before the accident. While the evidence supporting a traumatic origin of leukemia contains numerous shortcomings, these sources contain some information which may be of distinct value and serve as a guide for the handling and interpretation of similar cases in the future.

These data and considerations may be suitably presented with regard to the three possible relations which may exist between a trauma and a leukemia:

1. The presence of a leukemia is revealed through the trauma.
2. The preexisting leukemia is aggravated by the trauma.
3. The development of the leukemia seems to follow a trauma and may be etiologically related to it.

The interrelation between trauma and leukemia of the first mentioned type is solely coincidental, that is, the trauma neither plays a part in the causation nor influences the course of the leukemia. The case histories of this group usually contain a statement that a markedly enlarged spleen was discovered

immediately or soon after an abdominal trauma, especially of the left side. In some instances, in which the enlargement of the spleen was detected some weeks after the trauma, there existed pre-accidental pains of a rheumatic nature, pains of the bones, fatigue, dyspnea, and sensations of heaviness in the abdomen, or pains in the bones and along nerve trunks developed soon after a trauma resulting probably from leukemic infiltrations of traumatic hemorrhages. Such observations and symptoms indicate strongly that the leukemia in these cases was of much longer standing than the interval which elapsed between the accident and the discovery of the leukemic condition would suggest.

The coincidental nature of the trauma is even more strikingly displayed in cases in which the trauma results in an aggravation of the preexisting leukemia. Such cases are characterized sometimes by a marked disproportion between the severity of the injury suffered and the symptoms thereby produced. A minor trauma involving the splenic region may be followed by the appearance of severe pains caused in an enlarged leukemic spleen by tears of the capsule and hemorrhages, for which the leukemic changes furnish an exaggerated susceptibility. An acute myeloid post-accidental leukemia, showing the above related symptomatology in the presence of an enlarged spleen, represents, in all probability, an acute exacerbation of a preexisting, silent chronic leukemia, because an acute myeloblastic leukemia is usually characterized by the absence of an enlarged spleen and liver.

With the pre-accidental existence of the leukemia established, there may arise in some cases the question as to the aggravating effect of the trauma sustained. The difficulties encountered in this respect originate from the well-known observation that leukemias show spontaneously periods of lessened as well as heightened activity and progress. With due consideration of this fact the presence of a traumatic aggravation should be accepted when the accidental injury is followed directly by an appreciable and persistent aggravation of the leukemic symptoms (debility, dyspnea, incapacity to work, headache, dizziness, and hemorrhages). These reactions may assume a fulminant character and lead to death within a few days after the trauma, thus shortening the normal course of the disease. The most serious traumatic complications which may cause an activation of the leukemia are extensive hemorrhages, splenic injury, and infection. These conditions are known to be much more dangerous in a leukemic individual than in a normal person. In adjudicating such cases, it should be kept in mind that the prognosis of leukemia is invariably fatal and that death usually occurs in three to six years after the discovery of the disease. A unique traumatic aggravation of a leukemia was recorded by Scheuffler, who observed the development of a squamous-cell carcinoma of the skin after the traumatization of the site of a cutaneous leukemic infiltration.

The leukemias of the third variety, in which the trauma affected an indi-

vidual who, as far as could be ascertained, was in perfect health and alert up to the time of the accident, may be divided into two groups. The first group includes all those cases in which the trauma did not cause an open wound and did not result in an infection, but was followed, after weeks or months, by the development of a leukemia. In some cases there was a symptomless interval, lasting until the onset of the first leukemic reactions, after the direct traumatic manifestations had subsided. In two cases the first leukemic symptoms consisted in priapism (Rössler; and Liniger). In other cases a prolonged period of lingering and physical incapacity followed directly upon the traumatic episode, and gradually merged with the leukemic changes (Schimert; and Olshausen). The trauma present in this group of post-accidental leukemias involved the hematopoietic tissues directly through an injury to the spleen or bones, or indirectly through a general concussion. Olovson reported that in 40 out of 69 cases the trauma consisted in contusion of the abdomen (splenic region), in eight cases the accident had caused a fracture of some bone, while in 21 cases other regions were affected.

The second group of post-traumatic leukemias consists of cases in which the accidental injury resulted in an open wound with complicating infection. The leukemia developed apparently sometime after the onset and during the course of the infectious process (Hirschfeld; Steinhaus; and Curschmann). A chronic lymphatic leukemia existed in two cases, a chronic myeloid leukemia in a third (after an osteomyelitis of 14 years duration), and an acute myeoblastic leukemia in a fourth case.

The great majority of the cases of so-called traumatic leukemia are of the chronic myeloid type. There have been reported about seven cases of the acute myeloid variety (Yaguda and Rosenthal; Hirschfeld; Reckzeh; and Wittgenstein), and about an equal number of the chronic lymphatic type (Görtz; Greiwe; Norikoff; Yaguda and Rosenthal; Steinhaus; and Hirschfeld). Several attempts have been made to explain the marked predominance of the myeloid over the lymphoid type. It has been argued that the preponderance of the traumatic myeloid leukemias does not demonstrate any fundamentally different and increased reactivity of the myeloid tissue, but can be attributed merely to the fact that the myeloid tissue is subjected more often to traumatic influences than the lymphatic tissue. This reasoning may be applicable to the relative frequency of mechanical trauma in regard to myeloid tissue. When it is applied to the comparative incidence of chronic infections which affect more often and directly the lymphoid rather than myeloid tissues, it is scarcely correct. In commenting on this numerical discrepancy between traumatic leukemias of myeloid and lymphoid type, Schilling suggested that the apparent differences may be due to the fact that the lymphatic ones are usually recognized at a much earlier stage. The early and marked swelling of the superficial, palpable lymph nodes associated with lymphatic leukemia attracts the attention of the patient at an earlier

period. The swelling of the spleen (characteristic of myeloid leukemia) may escape discovery, since even a markedly enlarged spleen may not cause any appreciable subjective discomfort for a long time. Assuming that Schilling's explanation is correct, the circumstantial evidence against the traumatic etiology of leukemia is strengthened. It is doubtful whether clinical manifestations can account solely for the marked numerical discrepancy observed.

Traumatic leukemias occur more often in males than in females, which is in accord with the sex distribution of the cryptogenetic type. In a total of thirty-two cases, twenty-seven were in males and five in females. It is uncertain whether this observation indicates the presence of a greater susceptibility of males to leukemia, or reflects an etiological relation, that is, males are exposed more often to exogenous leukemiogenic agents.

Traumatic leukemias occur at a somewhat earlier age than the cryptogenetic leukemias. The traumatic leukemias are found in individuals ranging from 21 to 42 years (average 32 years) (Bousser), while the cryptogenetic leukemias are found most often in the age group ranging from 35 to 45 years. This observation is illustrated in the following table based on twenty-nine cases collected from the literature.

Age Distribution of Traumatic Leukemia

10–20	*21–30*	*31–40*	*41–50*	*51–60*	*61–and over*	*Years*
3.45	31.0	41.4	10.3	10.3	3.34	per cent
2	8	8	16	37	29	per cent chronic myeloid leukemia (Curschmann)
10	17	27	23	3	20	per cent acute myeloid leukemia (Curschmann)

This age relationship noted in traumatic leukemia when compared with cryptogenetic leukemia resembles that observed between spontaneous pulmonary tumors and those induced by treatment with tar or carcinogenic aromatic hydrocarbons in mice.

From an anlysis of the evidence presented the following conclusions may be drawn:

A. The great majority of so-called traumatic leukemias are represented by cases in which the relation between trauma and leukemia is coincidental, the leukemia being pre-existing.

B. A trauma may be considered, under certain conditions, as a factor aggravating the course of a pre-existing leukemia.

C. The actual occurrence of a "traumatic leukemia" (a leukemia primarily and mainly induced by a trauma) is neither amenable to scientific proof nor likely from our present knowledge of carcinogenic agents, unless the trauma brings about a condition in the organism, which in turn may act in preparing the soil for a secondary leukemic response in a predisposed individual. Chronic infections and perhaps severe traumatic circulatory disturbances in the spleen

may act occasionally in this capacity (Götsch). In all cases, in which such complications are not present, and in which a leukemia develops after an accidental injury in a heretofore healthy individual, trauma evidently does not create the fundamental leukemic reaction. It elicits this response from a prepared soil (an asymptomatic leukemic state) in a similar fashion as trauma sometimes provides the final stimulus for the manifestation of a roentgen-carcinoma in a skin conditioned for this growth lesion by previous exposure to the particular type of radiating energy. For those exceptional cases, in which a thorough and careful analysis of the pre-accidental symptoms and a critical evaluation of the post-accidental findings exclude with great probability the presence of a leukemia of longer standing, the existence of an etiological relationship between trauma and leukemia may be acknowledged in this sense. This decision does not settle the question from a scientific or medico-legal view point as to whether the trauma simply hastens the appearance of the blood dyscrasia, which might have become manifest normally at some later date, or elicits this response, which may never have become a reality without its intervention.

No evidence exists upon which to assume a traumatic activation of a leukemic virus, which may have remained silent and resting in the organism. The repeated failures to transmit mammalian leukemia by cell free filtrates militates against this conception. Human leukemia is not transferred from mother to fetus, which would likely occur if a virus infection were the cause of mammalian leukemia (Morawitz and Deneke), unless one assumes that some hypothetical, large molecular, leukemiogenic agent or the maternal leukemic leucocytes containing it were incapable of penetrating the placental filter. Experiments on pregnant leukemic mice were negative (Burchenal). It is unlikely that a direct blood contact with a leukemic individual might result in the transfer of leukemia. While the experimental introduction of mouse leukemic blood has been used successfully to transmit leukemia to normal animals (Furth), large amounts of leukemic blood have been transferred into individuals suffering with agranulocytosis without any untoward effects, in regard to subsequent leukemic developments (Schittenhelm; and Bock).

Finally, from a medico-legal standpoint it is essential that the diagnosis of leukemia should be established definitely and the organic effect of trauma demonstrated. The early and repeated examination of the blood furnishes some of the most important evidence. In the interpretation of the leukemic blood picture consideration should be given to the fact that occasionally cancer, tuberculosis, and septicemia may produce similar hematic changes. Roentgenograms of the bones should be made in all cases in which the development of leukemia after injury to these organs is made the subject of litigation. A complete post-mortem examination may contribute significant data by showing, for example, the site and extent of the injury sustained. In two of the traumatic leukemias reported large scars were shown in the spleen at

autopsy. The histological examination of the liver and spleen may provide definite proof of the existence of a leukemic process in cases of acute myeloblastic leukemia. In this disease these organs are not enlarged, but contain leukemic infiltrations, which are absent when the immature leukemoid blood reaction is caused by a septicemia or represents an acute traumatic phenomenon.

No evidence exists incriminating a nonspecific chemical trauma, such as exerted by exposure to war gases (chlorine, mustard, phosgene, and arsine), and the development of a leukemia (Gilchrist and Matz). No residual evidence of chronic myeloid or lymphoid leukemia was recorded from the 70,752 American soldiers reported to have suffered from gas poisoning during the late war.

Aleukemia. One of the main difficulties encountered in establishing definite correlations between trauma and leukemia is the fact that a chronic leukemia has a symptomatically silent preparatory stage which may last for several years. No information is available in regard to the developmental period at which definite leukemic changes, diagnostically important, become manifest in the blood. From the evidence at hand it must be assumed that the presence of such hematic deviations designates a rather late stage of the disease. It is obvious that the above difficulties will be multiplied in the case of an aleukemia, where a normal or subnormal number of leucocytes (leukopenia), containing immature and pathological cell forms, is found. The diagnostic uncertainty associated with this blood dyscrasia is probably the main reason that the literature contains only a few cases of aleukemia for which an etiologic relation with trauma is claimed (Döllner; and Kaltenschnee). In some instances of traumatic leukemia a primarily aleukemic condition may have been transformed by the action of a traumatic stimulus into a leukemia, a change which occasionally occurs spontaneously.

Döllner recorded a case involving an individual (male), who received a perforating gunshot wound (during the war, 1915) through the liver, causing a tear of the gall bladder. After recovery from the injury he did not attain his former good health, and six years later an enlarged spleen was found. The blood examination showed a moderate anemia and a mild leukopenia (5,500 leucocytes) with neutrophilia and immature myeloid cell forms. The diagnosis of an aleukemia was made and Döllner argued, in the ensuing litigation, that the dyscrasia developed after the injury, since an enlarged spleen had been absent apparently at the abdominal operation undertaken at the time of the war injury. The case was adjudged as compensable based on Döllner's reasoning, that the war wound of the liver had produced a disturbance of the hematic equilibrium normally existing between the liver and the spleen, thus causing the aleukemia. The decision appears to be justified from a medico-legal standpoint in view of the chronic character of the changes set up by the liver injury and its relation to the spleen.

Myeloma, Chloroma, and Reticular Cell Sarcoma of Bone. Myeloma,

chloroma, and reticular cell sarcoma (Ewing) are malignant neoplasms of the bone originating in the cellular elements of the marrow. The first two neoplasms possess, as a rule, primary multiplicity representing manifestations of a more or less systemic disease. The third type is said to start usually as a single tumor but, showing a tendency to secondary multiplicity, which is frequently restricted in its distribution to bony structures. It is still undecided whether some of the later appearing tumors are independent developments and thus systemic manifestations or are metastases.

Multiple myelomata, which occur in a plasmacellular, lymphoblastic, myeloblastic, and erythroblastic variety, and are comparatively rare neoplastic conditions, have been called a traumatic disease (Kahler), because of the frequent mention of a preceding trauma in the history of these cases (Isaac). Cases of allegedly traumatic myelomata were reported by Powchownik; Roman; Deutschländer; Ewald; Gluzínsky and Reichenstein; Heldt; Hirschfeld; Versé; Winkler; Simmonds; and Laesecke. The presence of a direct interrelation between the trauma and the development of multiple myelomata was claimed by Ewald; Gluzínsky and Reichenstein; Heldt; Versé; and Hirschfeld and Winkler, while Simmonds and Laesecke acknowledged that the trauma merely accelerated the course of a preexisting systemic myelomatosis.

The usual type of injury incriminated is a fall or blow against a bone, frequently resulting in a fracture. In the case reported by Simmonds the patient sustained a fracture of the humerus through a fall, and died three weeks later from pneumonia. The presence of a neoplastic condition was not suspected during the lifetime of the individual and the multiple myelomatosis, which was found responsible for the fracture, was discovered at autopsy. A noticeable growth at the site of the injured bone, beginning three days after the accident and within two weeks reaching the size of a fist, was observed by Ewald. Thus it was indicated that the accident had activated a preexisting myelomatous node into rapid proliferation. Similar circumstances were present in practically all other cases published, with the exception of the second of two cases published by Versé. In this case the evidence, supporting a causative interrelation between trauma and myeloma, deserves more serious consideration.

A blow against the costal arch of the patient resulted in a hemorrhage and a suspected fracture of the rib. The patient never did recover completely but started to ail. Three months after the accident severe pain developed in the back, which was soon complicated by the onset of a high fever. Five months following the accident a tumor formation was noticed at the site of the original injury. Death followed one month later, and the necropsy showed plasmacellular myelomas in the ribs, sternum, vertebrae, and iliac bone. The histologic examination of the tumor at the site of the injured rib revealed the presence of callus within the myelomatous tissue. Because of the relatively long interval which elapsed between the trauma and the clinical appearance

of the myeloma, in view of the continued illness since the accident, and in consideration of the presence of callus within the injured myelomatous rib, Versé concluded that the myelomatous condition originated from the contused rib tissue, and that an etiological correlation between the two events had to be assumed. Such a conclusion may be permissible from a purely medico-legal view point, in which circumstantial evidence must be accorded more weight than is possible when strictly scientific standards are applied. It is still difficult to reconcile such a conception with the fact that a local trauma to a bone is assumed to have initiated a multicentric, systemic neoplastic process of the myeloid tissues. Apart from the suggestion of Ewing that infections or nutritional disorders might play a role in the production of multiple myelomata, no information exists as to the etiologic factors operative in this respect.

While it is not very conceivable that a trauma to the bone might initiate a myelomatosis, sufficient evidence supports the conception that a myelomatous bone is affected more easily and severely by trauma than a normal one. Thus, it is readily understandable why minor injuries, which normal bones will withstand without serious effects, may cause a fracture in a myelomatous bone because of its rarified bony structure. This may lead to a local aggravation of the disease, and occasionally to a general hastening of its course by accelerating the proliferative neoplastic activity.

The allegedly traumatic myelomata do not differ essentially in symptomatology and biological behaviour from those of the cryptogenic type. Both occur during late adult life, fifth and sixth decade. The onset is usually quite sudden in both varieties, but occasionally a more insidious, gradual beginning is noted. Important warning signs are vague neuritic pains of a wandering, intermittent, or recurrent type, backache, progressive anemia, and spontaneous fractures. Short, flat bones, such as ribs, sternum, vertebrae, scapula, and skull, are affected most often by multiple nodules. Metastatic deposits may be found in the liver, kidney, lungs, and sexual glands. The spleen and lymph nodes are not enlarged usually. The demonstration of Bence-Jones protein in the urine is an important, though by no means constant, diagnostic sign. The prognosis is always hopeless, and the course after clinical discovery is rather rapid, causing death within two years in most cases. The traumatic myelomata have been so far exclusively of the plasmacellular type.

The case of a solitary myeloma of traumatic origin, reported by Beneke and Stieda, apparently belongs in a special class, since the possibility of an incorrect histological diagnosis exists. An encapsulated tumor developed in the frontal bone of a boy, ten years of age, following a fall. At its removal three months after the accident, it consisted of numerous vessels surrounded by masses of multinucleated giant cells and mononucleated cells of transitional cell type. The perivascular cells were small and round. Hemosiderin was present in some cells. The diagnosis made at that time was sarcoma and there was no recurrence. Three years later the boy fell again, on the other side

of the forehead, and a second tumor developed there. A roentgenogram made five weeks after the accident showed bony destruction. A tumor, about the size of a walnut, was removed surgically and consisted of myeloblastic and giant cells. The diagnosis was round-cell sarcoma of a myelogenous type, and the trauma was considered as the principal etiological factor. As in the first instance there was no recurrence.

Etiologically, histologically, and prognostically this case carries a certain resemblance to the benign, localized myelomata described by Mathias; Walthard; Rutishauser; and Geschickter and Copeland. These blastoma-like formations show a distinct similarity to the localized form of osteitis fibrosa. While a trauma apparently precipitated twice the formation of blastomatoid reactions of cellular elements of the bone marrow in a susceptible individual, these proliferative reactions do not belong to the group of multiple myelomata.

Chloromata, which are the second kind of relatively rare, systemic, multiple, nodular or diffuse, neoplastic, myeloid manifestations, have been connected repeatedly to a preceding trauma. According to a statement of Diez, the first case of an allegedly traumatic chloroma was reported by Hillier in 1853, and additional cases were published since that time by Chiari; Pfeiffer; Rosenblath; and Port and Schütz. In three of these four cases the condition developed in children, four to eight years old, which is the normal age range, while the fourth case (Port and Schütz) was observed in a sixteen year old youth. No information is available in regard to the occupational or non-occupational character of the injury, which allegedly precipitated the development of the chloromata, in the last mentioned case.

In the case recorded by Chiari the chloroma originated from the periosteum of the empty socket of a molar tooth, developing soon after its extraction and causing the death of the patient within three months. Chloromatous deposits were found in the bones of the extremities and the skull, in the bulbi of the eyes, and in the kidneys.

The history of Rosenblath's case reveals that within ten days after a fall on the ice a protrusion of both eyes of an eight year old boy was observed. During the brief course of the illness, which lasted only ten weeks, there developed a marked anemia simultaneously with a marked leucocyte rise (58,000). At autopsy chloromatous metastases were observed in the bronchial, tracheal, and abdominal lymph nodes and in the kidneys.

The history of a fall was present in the case reported by Pfeiffer. A four year old child fell on its left forehead and suffered an open but rapidly healing wound. Two months later a discharge developed in the right ear. This condition was followed by the development of an exophthalmos of the left eye during the third month after the accident, and some time later the same condition developed in the right eye. With the exception of a mild anemia the blood remained essentially normal. At the autopsy six months after the injury chloromatous deposits were found in both ocular bulbi, in the lymph nodes

of the neck, and in the periosteal tissues of the cranium. The histological diagnosis was made of chloro-lymphosarcoma.

The relation between the trauma and the chloromatous condition observed subsequently is mainly one of coincidental character. In the first case cited, the extraction of the tooth may have helped to produce a favorable soil for the development of a secondary deposit of the pre-existing chloromatous condition. In the other two cases, the trauma did not even affect the site of the first manifestation of the subsequently appearing chloromatous lesion. Since chloromata usually run a rapid course, it seems unlikely that the trauma influenced the course of the disease in these three cases.

The circumstances surrounding the fourth case of traumatic chloroma differ somewhat from those previously discussed. The individual affected was considerably older, and a prolonged infectious state, after an accidental contusion of a finger, preceded the chloromatous lesions. Two months after the injury, which finally necessitated the exarticulation of the infected finger, a slight elevation of temperature was noted. During the next month this was followed by the rapid development of a severe anemia (740,000 erythrocytes, 20 per cent hemoglobin), a hemorrhagic diathesis, a swelling of lymph nodes, and a marked leucocyte rise (44,000 cells, consisting of 70 to 85 per cent mononuclear cells, 8 to 15 per cent lymphocytes, and 8 to 9 per cent neutrophilic leucocytes). At death, occurring soon afterward, greenish deposits were found in the skull, and in the bronchial and tracheal lymph nodes. There was a mild myeloid metaplasia of the spleen and lymph nodes, while the bone marrow consisted of macro-lymphoid cells. The final histologic diagnosis was acute, chloromatous, myeloid leukemia.

In accordance with conditions discussed concerning the traumatic etiology of leukemia, the possible existence of etiologic relations between a trauma with subsequent infection and a chloroleukemia cannot be definitely excluded in this case; for the traumatic infection may have played an adjuvant role in the development of a leukemia in a predisposed individual.

Endothelial myeloma (Ewing) is a neoplastic disease of the reticular cells of the bone marrow. It occurs mainly during childhood (6 to 15 years), and usually affects the shaft of the long bones (especially the tibia) and the short and flat bones (vertebrae and pelvic bones) of Caucasians mainly (Connor; Ewing; Kolodny; and Lattman). A frequent point, in case histories reported, is a trauma (Copeland and Geschickter) preceding the neoplastic development by five and a half months on the average (Ewing; and Kolodny). Ewing maintained that a traumatic history cannot be reconciled easily with the origin of this tumor. He was inclined to concede to inflammation and infection (buccal and tonsillar infections) an etiological role. The age range of this tumor, which is relatively uncommon in individuals over thirty, restricts to a certain degree the possibility of an occupational traumatic relation to its development.

As the early symptoms produced by this tumor are characterized by intermittent pains in the bone, and attacks of fever, which may precede the recognition of the neoplastic cause by several months, it may be mistaken during this stage for osteomyelitis. The symptoms are of medico-legal importance in determining the duration of the disease and its time relation to any traumatic episode. No more definite and constant relation seems to exist between trauma and the origin of this myeloid tumor than that conceded to other types of neoplasms of leukopoietic cells. Sufficient evidence exists to indicate that a trauma to a bone affected with an endothelial myeloma may have an unfavorable influence upon the course of the disease by hastening metastases.

C. General Conclusions of Leucocytotic Reactions

In surveying the evidence presented one observation becomes outstanding: some of the chemical and physical occupational agents (aromatic hydrocarbons and roentgen-rays), which are involved in the causation of erythrocytotic reactions, are incriminated definitely or tentatively in the production of leukemoid, leukemic, and hematoblastic conditions. Apart from the existing identity or close resemblance of their chemical or physical qualities, they display a similar biological activity upon the leukopoietic elements of the hematopoietic tissues. This is evidenced by the fact that exposure to large quantities of these agents results in permanent aplasia, while contact with moderate amounts may cause, in most individuals, a transitory aplasia. The transitory aplasia is followed by an eventual recovery, occasionally passing through a hyperplastic phase, but producing in a few individuals an immediate, excessive regenerative response. The chances for such an overcompensatory, regenerative proliferation of one or the other type of leukopoietic cell even appears to be enhanced when a prolonged exposure to small doses of the causative agent takes place.

The occurrence of marked variations in degree and of divergences in type of the individual reactivity to similar doses of different agents, and the apparent presence of a sensitizing mechanism influencing these manifestations point to the existence of an allergic process contributing to their production. The observations presented are considered as sufficient indication for a thorough and diligent search in the occupational history of every leukemic patient for evidence of a prolonged contact with chemical agents affecting the leukopoiesis of the myeloid and lymphoid cells. Such an exposure may occur during the usual occupational activity, or it may be the result of a contact with certain medicines, cosmetics, foodstuffs with artificial colors, and flavorings. It would be logical to contend that, at the present time, only the most obvious and striking etiological interrelations of this kind have been discovered; and that a detailed analysis of the various exogenous factors just mentioned is bound to increase the number of known leukemiogenic agents.

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VII

OCCUPATIONAL AND ACCIDENTAL TUMORS OF THE MESENCHYMATOUS TISSUES

1. ANATOMICAL AND FUNCTIONAL CONSIDERATIONS

THE connecting, supporting, and special contractile tissues of the body composing the bony and cartilaginous tissues, ligaments, tendons, vascular elements, fat tissue, muscle tissue, capsules of joints, and the general fibrillar connective tissue are derived from the middle germinative layer, that is the mesenchyme or mesoderm. The only tissue of this type which is not mesodermal but ectodermal is represented by the notochordal tissue, found in the center of the fibrocartilagenous intervertebral discs. A characteristic feature for many of these tissues is the production of an intercellular substance of varying character forming a matrix in which the cells are embedded (bony tissue, cartilaginous tissue, fibrillo-fibrous tissue, and fibromucinous tissue). The general, fibrillar, connective tissue and the vascular tissues permeate all organs of the body and are ubiquitary in the body. A mesodermal tissue of wide distribution is the fat tissue. The occurrence of other types of mesenchymatous tissues mentioned is of a locally restricted nature.

The outer cutaneous and inner mucosal coverings of the body are composed of epithelial cells of ectodermal or entodermal derivation, respectively. It is obvious that exogenous, occupational agents can act upon these mesenchymatous tissues only in an indirect way, that is after their penetration of of the outer linings (resorption through the skin, or the mucous membranes of the respiratory and alimentary tracts, the mucous membrane of the urogenital tract not being normally involved in this respect as this system has an excretory or secretory function). A direct contact of the mesodermal tissues with exogenous agents is not possible under ordinary circumstances, unless there is a defect in the surface lining of the body. Physical agents, such as roentgen-rays and rays of radioactive substances, may penetrate the skin and act directly upon the underlying mesenchymatous tissues. Similarly, chemicals may act directly upon the underlying connective tissue after having passed through the epithelial surface cover.

Physical (radioactive substances) and chemical agents may establish contact with the various mesoblastic tissues, after they have entered the blood or lymph and have been transported to sites remote from their place of entrance. While in transit they are often phagocytized by certain cellular elements of mesen-

chymatous derivation, and moved in them actively or passively to distant regions. The physico-chemical properties possessed by various agents, such as fat solubility, chemical affinity to sulfur compounds and phosphates, determine the organs and tissues in which they may become finally deposited and concentrated, and in which subsequently neoplastic responses may be elicited, whenever carcinogenic agents are involved.

2. FIBRILLAR CONNECTIVE TISSUE

A. Chemical Agents

None of the various chemical agents which cause industrial neoplasms has been found to be involved in the occurrence of benign and malignant blastomas, originating from the common areolar connective tissue. This observation does not indicate that this tissue is refractory to the carcinogenic stimulus exerted by these substances. Abundant experimental evidence exists supporting the fact that some of these compounds as well as chemically closely related substances are well capable of eliciting such responses in animals.

Borst reported the development of a huge fibroma in the ear of a rabbit, which had been painted alternatingly with paraffin oil, tar and beta-naphthylamine solution following traumatization. An epithelial papilloma complicating this mesenchymatous tumor became ultimately malignant. Somewhat similar observations were made by Korényi, who noted in the ear of one out of ten rabbits, following repeated tar applications, the development of two nodes, one being a walnut-sized soft fibroma surrounded by a polymorphous cell carcinoma. Yamagiwa and Itchikawa obtained fibromyosarcomas in the breast of rabbits after intramammary injection of tar and tar dissolved in lanolin. The production of sarcomas in the subcutaneous tissue of rats following the injection of tar was reported by Russell. Löwenthal noted the development of two spindle-cell sarcomas in the diaphragm and in the parauterine tissue, respectively, of two out of 29 mice. These mice were injected intraperitoneally 12 times within four and a half months with the benzol soluble fraction of hard coal tar dissolved in olive oil. Among the teratoid tumors which Murphy and Landsteiner produced in chickens after the injection of embryonic pulp, two became sarcomatous after the introduction of tar. Choldin, who injected chickens subcutaneously with tar, observed in one instance the appearance of a polymorphous cell sarcoma. Similar results were obtained by Peacock; and Sturm and Murphy with subcutaneous injections of tar into chickens. While these neoplasms obtained were not transmissible by cell free filtrates, McIntosh obtained in 1933 four sarcomas in fowls by the injection of tar, three of which were propagated readily with filtrates. The sarcomas which appeared in pheasants after the injection of tar by Andrewes were not of the filtrable variety. When Andrewes, Ahlström, Foulds and Gye injected rabbits intravenously with tar and inoculated them

afterwards with fibroma virus a generalized fibromatosis developed in these rabbits, a result never obtained before with the injection of the virus only. Also, in one of the rabbits thus treated a non-transplantable, polymorphous-cell sarcoma appeared.

Numerous reports deal with sarcomas in subcutaneous tissue after the injection of the various synthetic carcinogens (3.4-benzpyrene; 1.2.5.6-dibenzanthracene; methylcholanthrene; 3.4.5.6-dibenzcarbazole; and o-aminoazotoluene) into mice, rats, and chickens (Andervont; Shear; Boyland and Mawson; Watson; Burrows; Barry and Cook; Boyland and Burrows; Peacock; Hieger and Kennaway; and Nishiyama).

B. Physical Agents

a. Radiating Energy—1. ultraviolet rays

While the occurrence of occupational solar carcinoma of the skin appears to be a well-established fact, there is so far no evidence available concerning the existence of sarcomatous responses in the skin of persons exposed excessively to sunlight. A number of investigators (Putschar and Holtz; Roffo; Beard, Boggess and von Haam; Huldschinsky; von Haam, Alexander and Beard; Büngeler; and Hueper), reported sarcomas in the skin of the ear, the ocular region, and the dorsum of the forefeet of rats and mice, usually in coexistence with carcinomatous lesions after prolonged exposure to solar rays and ultraviolet rays. It is not likely that this discrepancy in the behavior of the cutaneous connective tissue of man and certain animals reflects any fundamental difference in the sensitivity and reactivity of the connective tissue cells of various species to ultraviolet rays; but it is the result of differences in the structure of the human skin and the skin of mice and rats, and in the intensity of exposure present in man under natural conditions and in animals under experimental conditions. As the epidermis of mice and rats is very much thinner than that of man, and scarcely covered by horny layers which absorb strongly ultraviolet rays, these cancerigenic agents penetrate readily into the subepidermal connective tissue in rats and mice and thus may elicit sarcomatous responses. The thick, cornified human skin arrests the bulk of these rays within the epidermal layer. The degree of exposure to the solar rays existing under the most severe occupational conditions never approaches the high intensity and duration of ultraviolet irradiation to which the animals were subjected. This resulted in the production of actinic burns of a severity and depth unknown under occupational circumstances, and permitted a direct action of the ultraviolet rays upon the uncovered, subepithelial connective tissue.

The experimental actinic sarcomas of the skin, observed by Putschar and Holtz, were spindle cellular tumors or chondrosarcomas, when originating from the cartilaginous tissue of the ears. Roffo stated that 58.33 per cent of

the neoplasms produced in rats with the aid of solar rays and ultraviolet rays were sarcomas, while the others were carcinomas and carcinosarcomas. The skin of the mice in which Büngeler produced sarcomas by an intense exposure to solar rays had been sensitized by applications of hematoporphyrin, eosin, or anthrasol, respectively.

II. ROENTGEN-RAYS

Whereas the occurrence of occupational roentgen-carcinomas of the skin is not uncommon, the development of roentgen-sarcomas in the skin of persons exposed to these agents for professional reasons is very exceptional. There are so far only two occupational roentgen-sarcomas on record (Mulsow; and Unna). A third case reported by Porter and White is doubtful, as these investigators were uncertain whether they were dealing with a sarcoma or with a chronic granuloma. A fourth case, also of doubtful significance, is that observed by Gütig, who noted a fibrosarcoma in the scar of a roentgen-carcinoma located on the back of the hand, and surgically removed two years previously. The sarcoma noted by Unna was found in a worker employed in a roentgen-tube factory; Mulsow's case involved a physician (roentgenologist); while the doubtful case of Porter and White was seen in a roentgen-technician. The sarcomatous neoplasms were located on the fingers or hands, the skin of which exhibited the typical changes of chronic roentgen-dermatitis (epidermal atrophy and hyperplasia, pigmentary disturbances, and telangiectases) and simultaneously or subsequently roentgen-carcinomas. Roentgen-sarcomas form reddish, vascular nodes with smooth tips and verrucous marginal or basal portions, resembling in many respects as to gross appearance the roentgen-carcinomas (Hellner). The exposure period of Mulsow's case was twelve years. The two authentic cases of roentgen-sarcoma were spindle cellular fibrosarcomas displaying a moderate degree of vascularity.

Therapeutic Roentgen-Sarcoma. Occupational roentgen-sarcomas are thus relatively rare neoplastic sequelae of professional or industrial hazards, and constitute a very small fraction of the malignant cutaneous responses elicited by an occupational exposure to roentgen-rays (more than one hundred cases of roentgen-carcinomas have been recorded). Sarcomatous reactions after therapeutic application of roentgen-rays are by far more frequent, amounting to 12 per cent of the total number of therapeutic roentgen-cancers observed (Coenen).

The first cases of therapeutic roentgen-sarcoma were described by Perthes in 1904. Subsequent reports on neoplasms of this type were made by Alius; Pels-Leusden; Rosenbach; Deuticke; Kaplan; Hellner; Fischer-Wasels; Bohmer; Montgomery and Viecelli; and O'Donovan. The great majority of therapeutic roentgen-sarcomas were observed in connection with the roentgen-treatment of tuberculous lesions (lupus vulgaris and tuberculous arthritis, especially of the knee joint). Several roentgen-sarcomas have followed the roentgen-therapy of other conditions (psoriasis (Bohmer); sycosis

of cheek (Montgomery and Viecelli); hypertrichosis of cheek (Kaplan); and dural endothelioma (Deuticke)). Deuticke collected, in 1939, seven non-tuberculous, therapeutic roentgen-sarcomas, and found for these cases a latency period varying from 10 to 16 years. This compilation apparently did not include the case of Kaplan with a latency period of seven years, and that of Montgomery and Viecelli with a preparatory period of 30 years. The latency period for the tuberculous roentgen-sarcomas is from 5 to 20 years, according to Deuticke.

The incidence ratio of sarcomatous developments in a previously tuberculous tissue which was irradiated, as contrasted with sarcomas originating in a non-irradiated tuberculous tissue, is 45 to 10. The relationship of therapeutic roentgen-sarcoma on a tuberculous basis to the therapeutic roentgen-sarcoma of non-tuberculous genesis is 45 to 11, according to Deuticke. The combination of tuberculosis and roentgen-irradiation seems to favor the development of sarcomatous growths.

The causal connection between these conditions does not seem to be a direct one, as the sarcomatous development appears as a rule long after the tuberculous process has healed, and at a time when no tuberculous lesions can be found in the vicinity of the tumor. This suggests that the prolonged effect of the irradiation is the contributing factor rather than any specific effect exerted by the tuberculous tissue changes (Deuticke). This conception is supported by the fact, that roentgen-sarcomas have originated in nonspecific granulomatous tissues and chronic inflammatory lesions other than tuberculous ones.

In all these cases, the sarcoma developed as a late result of the irradiation treatment administered. The relative rarity of such neoplastic sequelae produced by roentgen-rays is attributed by Wyss to the natural inertness of the connective tissue. This investigator contended that roentgen-sarcomas develop on the basis of a radiation ischemia in the connective tissue. This assertion was disputed by Rosenbach, who observed in the bed of a roentgen-sarcoma a marked vascularization and no evidence of obliterative vascular changes. Roentgen-sarcomas are histologically fibrosarcomas, spindle-cell sarcomas, or polymorphous-cell sarcomas, the latter frequently showing a tendency to myxomatous transformations. The prognosis of roentgen-sarcomas is bad.

Experimental Sarcomas Produced by Roentgen-Rays. The causal rôle, which an excessive and prolonged exposure to roentgen-rays plays in the production of sarcomas of the connective tissue in man, has been confirmed by numerous experimental observations made in animals. Bauer; and Clunet, Marie and Raulot produced spindle-cell sarcomas in the cutis of rats, which had been exposed for up to 18 months to repeated treatments with roentgen-rays.

The presence of an accentuated reactivity of an inflammatory granulation

tissue to the sarcomatous effect of roentgen-rays was demonstrated experimentally by Burrows, Mayneord and Roberts; Lacassagne and Vinzent; Vinzent; and Lacassagne. The English investigators produced a noninfectious, inflammatory tissue in young rabbits by the injection of 3 cc. of olive oil, containing 10 per cent of powdered silica, into the pubic labia. The treatment was followed four days later by the injection of olive oil containing 2 per cent oleic acid. Some time after this administration, a 10 per cent watery suspension of kaolin was introduced and the resulting inflammatory lesions irradiated with 600 r. Spindle-cell sarcomas developed two years later in these areas in several of the rabbits thus treated.

The French investigators used chronic inflammatory foci produced by the subcutaneous inoculation of streptobacilli. The abscesses formed in the thighs of the rabbits thus infected were exposed to roentgen-rays (915 r), a treatment which was repeated five months later (455 r), and one year later (610 r). After the third application of roentgen-rays the abscesses receded gradually, followed after six months to three years by the development of sarcomas in five of the 27 rabbits used. One of the neoplasms formed was a spindle cellular fibrosarcoma, a second one was a rhabdomyosarcoma, and the other three tumors were osteogenic sarcomas. Similar results were obtained when two rabbits were injected in the mammary region first with diatomaceous earth, followed by the application of roentgen-rays. One of the rabbits developed a metastasizing fibrosarcoma, while the second animal showed an intracanalicular epithelioma of the mammary gland. Eighteen per cent of the animals thus treated developed malignant neoplastic reactions. It appears probable that a chronic inflammatory granulation tissue is more susceptible to a sarcomatous reaction when exposed to roentgen-rays, than seems to be the case with a normal quiescent connective tissue.

III. RADIOACTIVE SUBSTANCES

Apart from the occurrence of osteogenic fibrosarcomas in luminous dial workers, which will be discussed among tumors of the osseous tissue, no reports are available concerning the existence of occupational sarcomas of connective tissue origin, caused by an exposure to radioactive substances. There is only a single case of a therapeutic radium sarcoma of connective tissue genesis on record (Deuticke). This situation may change during the coming ten to fifteen years, as colloidal thorium dioxide solutions have been used during recent years for diagnostic purposes in man (Foulds). Neoplastic sequelae have not been observed so far in man (Selbie). Yates and Whitmore reported the absence of any neoplastic complications in 64 patients, who had received thorotrast (colloidal thorium dioxide solution) injections a few days to three years previous to autopsy. The intravenous or intramammary introduction of this substance has resulted, according to information available (Fleming and Chase; Stuck and Reeves; Harris; Naegeli and Lauche;

Lambin; Reis and Mesirow; and Romano and McFetridge), in fibrosis and parenchymatous atrophy of the liver, spleen, bone marrow, and breast. These changes may be attributed to the following threefold action exerted by thorium dioxide particles stored in the phagocytic cells of the body: 1. mechanical clogging of reticulo-endothelial cells; 2. metallotoxic effect upon these cells; and 3. radioactive action upon the phagocytic cells and their environment. The danger of late neoplastic sequelae, resulting from the medicinal use of thorium preparations, is aggravated by the fact, that it is difficult to obtain a pure preparation of thorium X. It usually contains small admixtures of mesothorium and radium (Laborde).

Experimental Sarcomas Produced by Radioactive Substances. Experimental evidence indicates that radioactive substances are very capable of eliciting sarcomatous responses in the connective tissue. Daels and Biltris embedded glass seeds, containing 50 mgm. of a powder consisting of radium sulfate and talcum in a ratio of 1:10,000, into the subcutaneous tissue of rats and mice, and found 12 months later in one out of ten rats thus treated a fusocellular sarcoma. A similar result was obtained in one out of ten rats into which had been implanted a glass seed containing radium bromide (0.1 to 0.3 cc. of a solution of 0.5 mgm. of radium bromide in 10 cc. of water). There was a fusocellular sarcoma present in one of the eight rats surviving for more than seven months. Three out of 38 mice similarly treated developed after 6 to 8 months fusocellular sarcomas of the subcutaneous tissue. When Ross implanted platinum tubes containing radium (0.1 mgm. radium element filtered by 0.5 mm. of platinum to obtain an almost pure gamma ray effect) into the thoracic wall of rabbits, he observed after 97 to 167 weeks six tumors in the nine survivors, three of these neoplasms being of the malignant connective tissue type (two spindle-cell sarcomas, one myxosarcoma). Mottram reported the production of sarcomas of the skin in two out of eight rats, which had received applications of radium to the skin.

One out of four chickens injected intravenously twice a week by Maisin and Dupuis with 2.5 cc. of a 1:10,000 solution of Ionium, which emits alpha rays at a relatively constant rate over a long period (14.5×10^4 half time), developed an intraabdominal fibroblastic sarcoma. Mottram exposed twelve chickens to 60 mgm. of radium over an area measuring 2 x 2 cm. located in the region of the chest or abdomen, respectively. The radium rays were screened through 0.12 mm. of silver, permitting the action of gamma and beta rays. The exposure time was 2.5 hours weekly in the beginning, and was later reduced to 5 to 30 minutes depending upon the condition of the skin. Of the five animals which died during the first 2.5 years of this treatment, three had sarcomas. One of them showed a keloid-like thickening of the skin, representing a spindle-cell sarcoma which invaded the lungs. The second animal exhibited, after 17 months of treatment, dilated ectatic vessels at the site of the radium application, while a fibrosarcoma was found underneath the skin

penetrating into the lungs and metastasizing into the abdomen. The third chicken had sarcomas in the irradiated area of the abdominal wall.

Special mention must be made of the production of sarcomas of the connective tissue by the experimental introduction of colloidal thorium dioxide, which is used under the trade name "thorotrast" for diagnostic visualizations of the liver, spleen, mammary glands, and brain (hepatosplenogram, encephalogram, mammogram, and ventriculogram) (Radt). The degradation products of thorium dioxide emit alpha rays, which are more penetrating than those given off by the radium series, and which are 10,000 times more injurious to tissue cells than the therapeutically used gamma rays. The amount of thorium dioxide commonly used for diagnostic purposes in man has an alpha ray activity equivalent to that possessed by 1.5 to 3 micrograms of radium (Taft; and Editorial, J.A.M.A.).

Roussy, Oberling, and Guérin injected 50 white rats intraperitoneally and subcutaneously, respectively, with a thorium dioxide solution. They found that after 10 to 17 months seven animals of the subcutaneous group had sarcomas at the sites of injection, while four survivors of the intraabdominal series of ten rats exhibited intraperitoneal sarcomas. There existed a direct relation between the dose of thorium dioxide administered and the incidence of tumors obtained: whereas 65 per cent of the animals injected with 2.5 cc. of the thorium dioxide solution developed sarcoma, 100 per cent of the animals exhibited such a result after the injection of 5 cc. of this agent. Some of the sarcomas were polymorphous-cell tumors containing cellular monstrosities, and were situated in the vicinity of thorium granules. Other intraperitoneal neoplasms exhibited the structure of fibrosarcomas containing numerous mitotic figures, and were attached to the omentum, mesentery, and wall of the intestine, that is, in regions of the abdominal cavity, where the thorium dioxide was apt to be precipitated and to settle because of its high specific gravity. The injection of 0.2 cc. of thorotrast into the nipple of nine guinea pigs was followed after three years by the development of neoplasms in four of these animals. Three of the tumors were fibrosarcomas, while the fourth was a carcinoma of the breast. Selbie injected 0.3 cc. of thorotrast subcutaneously into 60 rats and 0.1 cc. into 60 mice, repeating this procedure after two weeks. After 14.5 months there were fibroblastic tumors present in the subcutaneous tissue of 14 rats, while only two tumors (carcinomas) were found in the injected mice, one being manifest after nine months and the second 14.5 months following the injection of the radioactive agent.

IV. PHYSICAL TRAUMA

Benign Tumors: Fibroma. The traumatic genesis of solitary, benign, fibroblastic tumors (fibromas) is a controversial subject. While Würz contended that trauma is never involved in the causation of these neoplasms, Graef conceded that some of them might have a traumatic origin. Sontag and Ten-

deloo asserted that fibromas were usually the result of an injury to the connective tissue, and Ewing stated that fibromas of the periosteum and of the joints may follow a repeated trauma sustained by these tissues. Von Hansemann and other investigators looked upon fibromas as the products of some special type of inflammatory reaction of the connective tissue. Undoubtedly some of the fibromas (primary, genuine type), including the several varieties, such as fibro-lipomas, fibro-myxomas, fibromyomas, fibro-angiomas, and fibro-adenomas, originate from embryonic tissue misplacements and anlagen (kidney, breast, and uterus). Many others arise on the basis of preceding chronic, productive, inflammatory reactions in which other than fibroblastic elements may participate, possibly causing fibromatoid formations with various complex structures. A clear and definite distinction between early primary, genuine fibromas and fibromatoid, inflammatory, precursor lesions is made difficult, in that early fibromas are often not encapsulated and resemble in this respect productive fibromatoid proliferations, which merge insensibly with the tissues surrounding them. While true fibromas become encapsulated ultimately and appear as sharply circumscribed nodes, old fibromatoid inflammatory foci assume ultimately to an increasing degree neoplastic features, until they assume characteristics which make them undistinguishable from primary fibromas (Ribbert). It must be conceded, therefore, that a local trauma which elicits a chronic inflammatory process of the connective tissue may cause a solitary fibroma (Zipersson; Arning; Ricker and Gans; Fabian; Unna; and Gülden).

In addition to the frequent fibromatoid and adenofibromatoid formations occurring in the female breast, there arises rarely a peculiar type of myxofibroma, described as cystosarcoma phylloides or giant intracanalicular myxoma, which has been related in its origin to a preceding trauma to the breast. Lee and Pack stated that there was, in 13 out of 109 reported cases of this neoplasm, a definite and evidently authentic history of a trauma preceding the onset of the tumorous growth in the injured breast. These investigators were unable to decide, whether the trauma initiated the neoplastic development in these cases or simply activated a small preformed, but previously undetected fibroadenoma.

The development of multiple cutaneous fibromas has been related etiologically to a prolonged and severe exposure to low temperatures resulting in the production of frost bites (Zipersson). This investigator reported the case of a woman, 30 years old, who claimed to have sustained at the age of two numerous frost bites, which were followed by the appearance of multiple nodules in the skin. Some of these tumors were pedunculated and yellow brown, resembling in this way the neurofibromatous lesions associated with Recklinghausen's disease. It seems highly unlikely that any causal relations existed between frost bites and cutaneous fibromatosis, as alleged by Zipersson, as such multiple lesions develop evidently upon a congenital basis.

Keloid. Keloid is a peculiar blastomatoid excess formation of a hyalinized scar tissue, occurring in the skin after various types of traumas, but especially after burns, in predisposed individuals (Stout). Keloids are more common in females than in males, and are much more frequent in colored races (Negroes, Eskimos, Hindus, Malayans, Polynesians, Siamese, and Javanese) than in white races (Brenizer; Bohrod; Ewing; Fox; Matas; Hazen; Spitzer; Woolley; Steiner; and Linton). Balloch speaks for this reason of a fibroplastic diathesis of the colored races. The ratio of keloids in whites and Negroes is variously given as 1:9 (Fox; and Matas) to 1:14 (Hazen). Colored races use their congenital racial tendency for keloids in the production of cutaneous ornamentation of cicatrization (Malaysia and Australia). Individuals suffering from syringomyelia, causing trophic disturbances of the skin, exhibit a tendency to keloid formation (Müller). The degree of trauma which may elicit keloids varies considerably. Keloids may be formed in susceptible individuals after mild contusions which do not even cause a break of the skin (Lützeler). A single trauma is sufficient for a keloid response.

The most frequent sites of keloids are the anterior surface of the chest, face, neck, ears, breasts, hands, scapular region, and extremities; mucosal surfaces, such as the tongue, are involved only occasionally (Mook). They occur as single or multiple, and sometimes symmetrically situated, irregularly shaped, elevated, thickened, cicatricial formations having a smooth or corrugated, shiny, hairless surface and a reddish or white color. Telangiectatic vessels are frequently present in the skin of these formations, which vary markedly in shape (globules; nodules; plaques; lineous, elevated ridges; striae; cords; and ribbons), and from which processes of claw-like appearance may extend. The keloids in colored persons are either pigmented or white and devoid of any pigment. They are sometimes painful or elicit a burning sensation, and exhibit a hypersensitivity to pressure and heat. While they grow slowly in general, some display a rapid proliferation, and their maximum development may surpass ultimately the limits of the original lesion.

Keloids possess a characteristic histological structure. Keloids start as round cellular growths in the adventitia of the arterioles in the corium. These round cells become later fusiform and produce fibrils (Ormsby; and Heidingsfeld). Well developed keloids show the following structure: Beneath a normal, or in older cases atrophic epidermis, sharply defined, thick, hyaline, interlacing and anastomosing, wavy and whirly bundles of collagenous fibrils are found forming a matrix, in which numerous well-preserved fibroblasts are interspersed. The whirly configurations are located in the adventitia of the vessels. The fibrillar bundles run for the most part parallel to the surface of the skin. Young keloids are more cellular than old ones, and have cells with long oval bodies and large vesicular nuclei often undergoing mitosis. Numerous small blood vessels and lymphatics, the latter sometimes cystically distended, are found in the keloid, giving it an angiomatoid appearance. The

vessels usually possess several layers of endothelial cells. An infiltration with mast cells is found frequently. There are no argyrophile or elastic fibrils in the keloid. The keloid growth is restricted to the corium and does not involve the papillary body, but may cause its atrophy by pressure exerted upon it, leaving only a narrow band of normal, connective tissue between the epidermis and the keloid. The keloid grows expansively by pushing aside the cutaneous appendiceal organs located in the corium. The periphery of the keloid is not sharply defined. There is a sort of capsular demarcation toward the normal tissue, formed by a cellular fibroblastic zone, which is accentuated in older keloids by the presence of surrounding compressed tissue. Extending from the central main mass of the keloid, strands of cells accompany the blood vessels into the extrakeloid tissue. It is from these groups of cells that recurrences are formed after surgical removal of the main keloid mass. Keloids may assume occasionally a neoplastic character (Ewing; Porter; and Biberstein).

Dupuytren's Contracture of the Hand. Although a great deal of controversy still exists concerning the rôle which heredity plays in the production of the fibromatoid scarring of the palmar and plantar aponeurosis (Deckner; and Reichle), there does not seem to be any doubt that occupational trauma represents an important etiological factor in bringing about this condition, which has been recognized in Holland and Russia as an industrial disease. Dupuytren's contracture is found chiefly in certain types of workers doing heavy manual labor (Dupuytren; Ewing; and Schröder), involving repeated excessive stretching of or blows to the palm of the hand. Epstein noted that this condition was often observed in glass blowers, who handle long hot iron blowpipes and sustain frequent burns in the palms of their hands followed by scarring. Recent investigations of Teleky showed that this fibromatoid degeneration of the palmar aponeurosis occurred in 17 per cent of the calenderers of weaving mills who were over 40 years old and had been employed for 15 to 20 years. In persons belonging to the white collar class, this particular ailment may be elicited by sporting activities (Schnitzler). In addition to repeated occupational trauma, solitary accidental injuries to the palm or adjacent tissues may lead to the development of the contracture. Kohlmayer reported that this condition develops in 1.5 per cent of the cases of radial fracture caused by a traumatic tear in the palmar aponeurosis, complicated by hemorrhages and trophoneurotic disturbances.

The tissue causing this fibromatoid scarring consists of large spindle-shaped cells of rather embryonal appearance, resembling to some extent immature muscle cells. This fact has been considered as evidence supporting the conception that the contracture originates on the basis of an embryonal tissue malformation. The palmar tissue usually contains a myxomatous or desmoid component, thus exhibiting histological features not infrequently observed in contractures of the palm of neurogenic origin, and probably being the reason

for the conception of Ewing, who considers Dupuytren's contracture of the palm a traumatic neurofibroma. Meyerding, Black, and Broders called attention to the histological similarity of the tissue of Dupuytren's contracture with fibrosarcoma, the sarcoma-like areas being located in the palmar fascia at the site of the nodules characteristic of the disease.

Malignant Tumors: Sarcomas. The appearance of malignant neoplasms (sarcomas) in areas of previously traumatized connective tissue has been reported repeatedly, and has been made the subject of allegations concerning the existence of a causal relationship between the two events (Coley). In refutation of such claims Simon; and Winkler have pointed out that regions especially exposed to physical injury (buttocks, knee, sole, and breast) are relatively rarely the seat of sarcomas. Theilhaber noted the great rarity of traumatic tumors, including sarcomas, of the hands, feet, and particularly of the soft tissues of the pelvis, where birth traumas are frequent, repeated, and very severe. The topographic distribution of sarcomas does not run parallel with the local incidence of traumatic injuries.

The development of allegedly traumatic sarcomas of the connective tissue may be a delayed phenomenon, that is, the sarcoma originates apparently from a previously formed, fibromatoid, cicatricial tissue, or it is a relatively early and direct sequela of the cellular reactions elicited in the injured tissue. The acceptance of a causal relationship between a previous trauma and the sarcomatous manifestation is made easier, if histological evidence can be obtained demonstrating various developmental steps between an inflammatory, fibrous, granulation tissue or a traumatic "fibroma," and the sarcoma present at the site of such changes (Halkin; and Becker). Such malignant transformations of traumatic, fibromatoid reactions are comparatively rare (Simon). Histological changes frequently observed in a chronic, inflammatory, granulation tissue may simulate those found in fibrosarcomatous lesions. The histological evidence upon which the claim of a traumatic "sarcoma" is based should be examined carefully and critically, supported by signs of definitely infiltrative growth, and, when possible, by the presence of metastases and rapid recurrences after surgical removal of the tumor before the diagnosis of malignancy is warranted.

The existence of scar sarcomas or fistula sarcomas, which develop through a gradual transformation of fibromatoid scars into hard fibrosarcomas, usually in the course of three to four years after the injury (Lubarsch), is attested by a moderate number of case reports. Philippsberg recorded the case of a soldier who had sustained a wound in the soft parts of the back by a shell splinter. Two years after the injury a nodular mass appeared in the scar, which was surgically removed, but recurred within a year and a half. After the extirpation of the second node, a rapidly growing mass developed from the scar which exhibited in places the structure of a cellular fibroma, while in other parts it had the morphology of a fibrosarcoma. Lützeler reported the

occurrence of a polymorphous-cell sarcoma, originating in the scar of a wound in the upper arm caused by a shell splinter 18 years previously. Loenhard recorded the appearance of a spindle-cell sarcoma in the buttocks of a man, 27 years old, who had been injured in this region one year previously by a blow against a rail. A tumor, which developed five years after a basal fracture in the posterior superior nasal fossae, showed upon histological examination the structure of a fibroma growing from a fibrous scar exhibiting sarcomatous areas in places (Portmann and Davis).

The occurrence of sarcomas of the breast has been related often to a preceding injury to this organ (Vogel; and Rose). Sarcoma of the breast is found more often in men than in women, in spite of the fact that the female breast is certainly much more often subjected to trauma than the male [about 2 to 7 per cent of all mammary cancers in women are sarcomas, while approximately 14 per cent of mammary cancers are of sarcomatous type in men (Rose; and Winkler)]. Apart from this observation, which does not seem to favor the existence of a traumatic origin of breast sarcomas, consideration should be given to the fact that the connective tissue of the female breast participates in the rhythmical menstrual changes of this organ, being for this reason in a status of cellular instability which should predispose rather than hinder sarcomatous responses. Winkler, who is aware of this apparent inconsistency, argued that a trauma to the large female breast produces, in contrast to the effect observed in the male breast, diffuse necroses with subsequent scar formation, which in turn propagates through the resulting tissue anemia a carcinomatous growth rather than a sarcomatous one. All claims of a traumatic origin of mammary sarcoma must be viewed with a great deal of reserve.

A case of traumatic sarcoma reported by Lecène and Lacassagne deserves special mention, as it involves the combination of a local occupational trauma with a possible direct transmission of a carcinogenic agent. These investigators reported a spindle-cell sarcoma in the palm of a surgeon, following a prick with a needle contaminated with the serous fluid coming from the wound of a breast amputated for carcinoma. Lecène and Lacassagne suggested that the sarcomatoid tumor originated from an accidental inoculation of carcinoma cells into the tissues of the palm, and that the resulting spindle cellular neoplasm was actually a carcinoma because it behaved biologically like one (metastatization by way of the lymphatics). Whereas the accidental origin of this unique case of occupational sarcoma cannot be doubted, the argument advanced in support of its carcinomatous character is not convincing for two reasons: 1. sarcomas of the extremities metastasize frequently through the lymphatics; and 2. the experimental transplantation of mammary cancers of mice has given rise to sarcomatous growths originating apparently from the connective tissue surrounding the implant.

3. MUSCULAR TISSUES

A. Leiomyomatous Tumors

Ordinary occupational activity and contact with industrial agents have no etiologic relation to the development of tumors of the smooth and striated muscle tissues. While leiomyomas (fibromyomas and fibroids) of the uterus are very common tumors [40 per cent of all women above 40 years of age are said to have such neoplasms (Corscaden and Stout)], benign and malignant blastomas of both muscle types are rare in other organs (Geschickter and Maseritz). It is assumed that uterine myomas are of dysontogenetic or hormonal origin. Uterine myomas and adenomyomas are claimed to be derived from misplaced rudiments of the mesonephros or Wolffian body, and have been found to be dependent to a certain extent in their proliferative activity upon the function of the ovaries. Congenital malformations and misplacements are incriminated for the production of the solitary or multiple leiomyomata of the cutis and subcutis, found especially in the mammilla, labia majora, and scrotum, and showing a symmetrical or asymmetrical distribution. Leiomyomas of other organs (stomach, intestine, bladder, and prostate) are rare. Malignant leiomyomas and leiomyosarcomas are so rare that they are of little practical significance (Gardner; Cohen; and Ewing). It is stated by Hertzler, that a malignant transformation of uterine leiomyoma may be brought about by a hemorrhage into the tumor tissue.

B. Rhabdomyomatous Tumors

Similar considerations apply to the rhabdomyomas and rhabdomyosarcomas, both of which are seldom observed in man, and involve only rarely the skeleton muscle [in only 15 cases out of a total of 223 extracardiac rhabdomyomas (Ono)]. The age distribution of the cardiac, blastoma-like formations as well as their common coexistence with other tissue disturbances of a congenital nature point to their dysontogenetic origin. Rhabdomyomas and rhabdomyomatosis (rhabdomyoblastoses) of the heart are observed as a rule in children and less often in young adults. They are frequently associated with cerebral gliomas, sebaceous gland adenomas, and renal adenomas (Steinbiss; and Hueper) and are not a true neoplasia, but a hyperplastic congenital malformation. Adenorhabdomyosarcomas of the kidney occur in young children; grape-like rhabdomyosarcomas of the vagina and vaginal cervix are found during the same age period; and rhabdomyosarcomas of the orbit are seen during the first ten years of life (Montpellier). The development of rhabdomyosarcomas of the ovary, bladder, breast, prostate, testis, and lung is restricted almost entirely to the first three decades of life. Even the rhabdomyomas of the tongue and skeleton muscle exhibit a preference for this age period (rhabdomyoma of the tongue: 10 cases; seven occurred in individuals 1 to 30 years old, three appeared later; and rhabdomyoma of the skeleton

muscle: 16 cases; eight developed before the age of 30, while the same number appeared in individuals who had passed this age). A striking exception from this type of age distribution is offered by the rhabdomyosarcomas of the uterus, which involve only women more than 30 years old (peak between 40 to 60 years), suggesting thereby a different type of genesis.

In view of this evidence supporting a dysontogenetic origin of rhabdomyomatous neoplasms, the repeated observation of cases, exhibiting a certain causal relationship to a preceding trauma, is of special significance. Müller reported the occurrence of a rhabdomyosarcoma of the thigh in a man 48 years old after repeated fractures of the femur (first at 4 years of age, second at 11 years). Twenty-seven years later a rhabdomyosarcoma was found at the site of the callus. The tumor originated from the surrounding muscle tissue. A malignant myoblastoma of the forearm was seen by Ono in a soldier 24 years old, who had received a stab with a bayonet. The tumor developed within one month after the accident. Ono noted that the malignant rhabdomyomatous neoplasm developed from a derailment of a regenerative muscular proliferation. Charache recorded the appearance of a rhabdomyosarcoma in a man 44 years of age, following a contusion of the thigh due to a fall. A tender, blue lump appeared one week later, and grew progressively to the size of a grapefruit, causing widespread metastases. Derman and Golbert claimed trauma to the tongue as a causative factor in the development of lingual rhabdomyomas. In reviewing 75 cases of sarcoma of the skeleton muscle, Shanin found that trauma and infection seemed to be predisposing factors in some of these cases. It was stated by Küttner that a dull trauma may initiate the development of sarcomas from skeleton muscle, the great majority of which are not rhabdomyosarcomas, but undifferentiated round and spindle cellular tumors. Geschickter and Maseritz, who analyzed a series of 19 striated muscle tumors involving the body wall or the extremities and including 13 undifferentiated rhabdomyosarcomas, noted that a traumatic history was present in only one case. While the age distribution of these cases (0, 21, 35, 40, 43, 36, 45, 46, 52, 52, 62, and 68 years) favors the existence of an exogenous and possibly traumatic etiologic agent, the sex ratio (nine females, seven males) militates against such a conception.

C. Myositis Ossificans

The cellular reactions seen in traumatic myositis exhibit sometimes a close morphological resemblance to sarcoma. Ewing noted that an injury to the muscular tissue does not constitute an essential contributory factor for changing these pseudosarcomatous lesions into truly malignant ones. Brief mention may be made finally of the occurrence of traumatic heterotopic ossifications in the skeleton muscle, which ensue from the interstitial connective tissue by a process of indirect metaplasia. Their development depends apparently upon the production of circulatory disturbances (hematomas), in combination with

destruction of the specific muscular elements and their replacement by connective tissue. Local imbalances of the calcium metabolism bring about subsequently the transformation of fibroblasts into osteoblasts. These tumor-like bony inclusions of the skeleton muscle are seen frequently in horsemen (rider's bone involving the muscle tissue of the inner aspect of the thigh) and in soldiers ("Exerzierknochen" involving the region of the shoulder) (Delbet and Brault; and Bürkle-de la Camp). They are seen occasionally in other parts of the body, as the result of traumatic influences to the muscle and joint capsules (dislocation of shoulder or elbow joint, especially). Such areas of ossifying myositis are composed of normal bony tissue and atypical cartilage, but exhibit occasionally atypical osseous tissue and very atypical cartilaginous tissue, such as seen in osteogenic sarcoma, thereby imitating closely sarcomatous growth and frequently being mistaken for it (Ewing).

D. Desmoid Tumors

The so-called desmoid tumors most often observed in the abdominal rectus muscle of women, between the age of 20 and 50 years (87 per cent of these tumors found in women) following pregnancy, possess presumably a traumatic genesis (Scudder; Ewing; Knox; and Carranza and Arenas). These hard; fibromatous, nodular formations are the reaction products of traumatic contusions which occur in the rectus muscle as a sequela of accidental injury or as the result of muscular laceration after excessive stretching and subsequent degeneration of the muscle tissue. These are complicated by a prolonged interference with the normal healing process by constant traction exerted upon the injured area during the period of gestation. Inasmuch as similar fibromatous manifestations have been observed in the same location, but on an apparently congenital basis, it is assumed that a special individual predisposition is essential for eliciting a traumatic development of these desmoid tumors. They do not display any tendency toward a malignant transformation.

E. Experimental Tumors of Muscle Tissue

In contrast to the great rarity of rhabdomyomatous neoplasms in man under any circumstances, these tumors are produced relatively readily in rats by the injection of 1.2.5.6-dibenzanthracene (Woglom). Haagensen reported the development of rhabdomyosarcomas, leiomyosarcomas, and undifferentiated sarcomas in mice and rats after the injection of the same chemical. Myoblastic neoplasms were obtained by the experimental introduction of tar. Löwenthal noted the appearance of a myoblastic sarcoma of the pylorus in a mouse following the intraperitoneal injection of tar. While the inoculation of the Rous' agent into the pectoral muscle of chickens sometimes resulted in the development of myoblastic growths (Peyron), the injection of tar was followed by the appearance of fibrosarcomas (Murphy; Peacock; and McIntosh).

There exist a few reports on the experimental production of muscular neoplasms in animals by physical agents. Beard, Boggess, and von Haam mentioned the occurrence of leiomyosarcomas in rats, which had been exposed to a prolonged irradiation with ultraviolet rays. Vinzent; and Lacassagne and Vinzent recorded the development of a rhabdoymosarcoma from the muscle of the thigh in a rabbit, eleven months after the inoculation with streptobacillus caviae followed by a local irradiation of the abscess formed with 610 r. The investigators attributed the tumor formation to the combined action of the infection and the roentgen-ray treatment. The action of metals (tin) in conjunction with physical trauma was blamed for the appearance of a spindle cellular sarcoma in the gluteal muscle of one out of 27 rats into which pieces of various foreign materials had been implanted (wood, copper, zinc, tin, brass, lead, and clay), and which had been subjected afterwards to additional traumatism by being placed twice a week into a rotating drum (Larionov).

4. VASCULAR TISSUE

Proliferative reactions of the vascular tissue in response to occupational influences may take the form of simple dilatations of preexisting vessels, often combined with some degree of hyperplasia of the vascular elements (telangiectases and varicosities) or they may assume a neoplastic character (hemangioma and hemangioendothelioma).

A. Telangiectases and Varicosities

Ectases of the veins and capillaries in the subcutaneous tissue, usually associated with a more or less marked degree of tortuosity, are seen many times in individuals whose occupational activities require them to stand for prolonged periods (clerks, nurses, and laundresses), and who develop varicose veins because of excessive and prolonged mechanical static strain exerted on the venous walls of the lower extremities. Persons with a sedentary occupation are apt to acquire hemorrhoids representing local, nodular, or polypous dilatations of parts of the perianal venous plexus for similar static causes, often accentuated by constipation.

The occupational exposure to certain physical and particularly actinic agents (solar rays, ultraviolet rays, roentgen-rays, and radioactive substances) and to several carcinogenic chemicals (arsenic and tar) may result in the development of simple convolutes of angiectases in the subcutaneous tissue. These changes in the preexisting superficial capillaries of the corium are partly of functional origin (loss of contractibility), and partly caused by proliferative and obliterative processes elicited by these agents in the larger and deeper veins, producing localized circulatory disturbances (Windholz; Wood; and Wohlbach).

While a blastomatous transformation of these cutaneous hemangiectases has not been observed after occupational exposure to the above-mentioned physical

agents, Ross reported a case of a malignant hemangioma of the liver, which he attributed to the actinic effect exerted by a radium needle. This needle contained 2 mgm. of radium element screened by 0.5 mm. of platinum, which had been introduced four years previously into the breast of a woman, 44 years old, in the treatment of cancer of the breast. This needle had not been recovered from the breast at the end of the therapeutic period, but had migrated and had become lodged in the pericardium close to the liver. The cavernous hemangioma formed subsequently in the liver opposite the site of the needle was composed of anaplastic endothelial cells, and originated from the sinusoidal endothelium of the portal vein in an atrophic area of the liver, located near the needle. Ross noted that this case was unique in so far as it represented the only instance in which adequately screened radium had caused by prolonged exposure the development of a malignant neoplasm.

B. Traumatic Hemangiomas

Neoplastic manifestations of the vascular tissue are characterized by the new formation of vessels in addition to their longitudinal growth. Angiomas, which may be found in all organs with the exception of the cornea and cartilage, have been related genetically to congenital malformations by most investigators (vascular nevus of skin and Lindau's disease of cerebellum and retina). Hemangiomas occur predominantly in young individuals. This fact is well-established, particularly in regard to the proliferative manifestations displayed frequently by vascular nevi during the early years of life. In a review of 256 cases of benign angiomatous tumors of the skeleton muscle, Jenkins and Delaney found that 79 per cent of these neoplasms were observed in individuals before the age of 20 years, and 94 per cent in individuals less than 30 years old. Bennett and Cobey, reporting 5 cases of hemangioma of joints, stated that the age range was from 18 months to 18 years. While a congenital factor seems to be of main importance in the etiology of the great majority of these tumors, there exist reports of cases in which a certain causal relation of the formation of angiomatous tumors to mechanical trauma (Jenkins and Delaney; Davis and Kitlowski; Downing and Mallory; and Löwenthal) is suggested.

Jenkins and Delaney found in their review of muscular angiomas a traumatic element recorded in 43 cases (17 per cent). The most frequent site was the thigh. In his treatise on the relation of trauma to tumor formation, Löwenthal listed 10 traumatic angiomas, two of which were malignant. In the first case of traumatic endothelioma reported by Löwenthal, the neoplasm developed in the hand of a boy who was 14 years old, when he was bitten by a dog. There had been at that time a large hemorrhage. While the presence of the tumor manifested itself in the beginning only by a sensation of pressure, it had grown into a tumor seven years later and involved the forearm, when the boy was 25 years of age. The second case was found in a woman 19 years old,

who had struck her bare heel on a stone 8 years before. A tumor developed at this site and spread to the external malleolus and to the toes. In a third case of alleged traumatic endothelioma, which is of more recent date and which was reported by Downing and Mallory, a soldier, who had been hit by a shell splinter in the left side of the neck and shoulder in 1918, developed three months following the injury a deep-seated swelling of the neck, after the superficial abrasions had healed readily. The swelling increased in size and became gradually covered with red and blue spots and nodules, composed of telangiectatic vessels. New lesions continued to appear. Upon excision the neoplasm was shown to be an endothelioblastoma invading the lumina of veins and penetrating into the surrounding muscle tissue. As there had been no evidence of a preexisting vascular abnormality, it was assumed that the endothelioma was the result of a traumatic arteriovenous communication. The increased pressure exerted upon the walls of the small veins was thought to have caused an excessive stretching of these elements together with a dilatation of the venous lumina. Secondary endothelial proliferation and vascular sprouting stimulated by these conditions ultimately got beyond control and led to the neoplastic end result.

It is sometimes difficult or even impossible to distinguish clearly between traumatic angiomatous responses and hyperplastic, regenerative, vascular proliferations in organized hematomas [telangiectatic granulomas (Coenen)]. This situation is illustrated by a case recorded by Mailer. The description mentioned the development of an angiomatous tumor two months after the bruising of the triceps muscle. It is significant, concerning the developmental mechanism and character of the vascular proliferation observed in the injured muscle, that it seemed to originate from the wall of an intramuscular hematoma and to consist of a hyperplastic proliferation of capillaries and small arteries. It is doubtful whether these vascular convolutes represented actually a hemangioma, or were an extraordinary response of vascular elements of a regenerative and resorptive character, elicited and stimulated by the blood clot. Injured blood vessels may regenerate in an atypical fashion by forming large varicosities and open spaces lined by endothelium, which ultimately assume the character of hemangiomatous formations (Andrei).

The experimental production of angiomas was accomplished by several investigators. Löwenthal reported an endothelio-sarcoma of the liver in a mouse following intraperitoneal injection of tar. McIntosh observed the appearance of endotheliomas and angio-endotheliomas among other tumors in the pectoral muscle of chickens after the intrapectoral introduction of tar.

C. Angiomyoneuromas (Glomus Tumors)

The relatively uncommon tumors of the glomus [the arteriovenous short cut of the skin important for the regulation of body temperature (Popoff)] show a frequent causal relationship to trauma, according to the data recorded

in the literature. In 30 to 50 per cent of the more than one hundred cases described (Saccone and Mendeloff) a local trauma preceded their development (Grauer and Burt; Masson and Barré; Prodanoff; Thomas; Lewis and Geschickter; Jirka and Scuderi; Mason and Weil; Martin and Dechaume; Bailey; and Raisman and Mayer). They occur as bluish to bluish-black discolorations of the skin, measuring up to 2 cm. in diameter, and forming small cutaneous elevations. The glomus tumor is highly sensitive to pressure, which causes excruciating pains radiating up the affected extremity and being accentuated by changes of temperature, particularly cold. They are found mostly on the hands and feet, especially beneath the nails, where they may be mistaken because of their color for subungual melanomas. Other sites are the arms, prepuce, and thigh. Multiple glomus tumors were noted occasionally (Bergstrand; and Weidmann and Wise). The two sexes are affected equally often. The age range extends from one to 80 years. The neoplasm, which is usually encapsulated in contrast to the ordinary angioma, consists of many long, distended, angioma-like, vascular spaces lined by endothelial cells. Numerous polyhedral cells with pale staining, reticular-like cytoplasm, containing a deeper staining nucleus (epitheloid cells), occupy the extravascular areas which contain neuro-reticular matter. In commenting upon the high incidence of trauma in the causation of glomus tumors, Grauer and Burt raised the question, whether there might not be a congenital weakness in the glomus bodies in the affected individuals, which manifests itself in an overdevelopment after a traumatic injury, producing what is recognized as a glomus tumor. This conception regarding a congenital contributory factor receives some support from the fact, that these neoplasms are especially frequent among members of the Jewish racial mixture (Stout). This investigator suggested that the predominance of disturbances of the sympathetic nervous system in this racial group may be a factor in explaining the comparatively high incidence of glomus tumors among Jews.

5. ADIPOSE TISSUE

A. General Anatomical Considerations and Classification

Tumors of the adipose tissue consist of cells containing neutral fats and lipoids, and belong to the most common types of neoplasms (4 to 5 per cent of all benign newgrowths). They are found more often in females [73.1 per cent (Adair)] than in males. The great majority of these blastomas are of benign character, and truly malignant tumors of the adipose tissue (liposarcomas) are relatively rare. This situation is noteworthy as the fat tissue represents a storehouse for many of the known organic carcinogenic chemicals, these being, in general, fat soluble.

The classification of cellular proliferations, characterized by a high fat or lipoid content of the component elements, is complicated by several factors.

The demarcation between benign tumors of fat cells (lipomas) and simple or complex, localized or diffuse hyperplasias of these cells is not always sharp, and transitions between various proliferative manifestations of the adipose tissue occur. The histological similarity is especially close in the case of regenerative or inflammatory hyperplasias, in which young fat cells with their foamy cytoplasm are prominently present. Fat cells may represent an integral part of more complex benign tumors, such as fibrolipomas, angiomas, neuromas, and neurofibromas (here usually of the lipoid or xanthomatous type) (Payr; Harbitz; Koettnitz; Agadjaniantz; Harvey; and Stewart). A high lipoid content is characteristic of certain benign and malignant neoplasms of the suprarenal gland (hypernephromas), and may be found often as a more or less generalized feature in numerous other tumors, especially of the malignant type (mammary cancers and renal carcinomas), causing a xanthomatoid transformation of the cellular structures. These observations merit proper consideration in any case involving the possible relationship between occupational activity and the causation of blastomas of the adipose tissue.

While the causes of some of the diffuse localized or diffuse generalized accumulations of fat tissue are known (endocrine disturbances, excessive food intake, and dystrophic replacement of other tissues by fat tissue), the etiology of the circumscribed neoplastic formations of adipose cells is largely obscure. Ewing favors the view that lipomas develop from embryonic anlagen, each possessing its independent system of blood vessels, in the meshes of which the fat tissue forms by infiltration of perivascular cells. He points out that the lobulated structure of lipomas reflects their histogenesis. Other investigators credit congenital disturbances of the nervous system causing trophic changes with an important rôle in the production of these tumors, especially of the multiple variety. No evidence has been advanced so far supporting or even suggesting an occupational genesis of neoplasms of the fat tissue.

B. Experimental Production of Tumors of the Fat Tissue

Recent experiments of Haagensen and Krehbiel have shown that the cells of the adipose tissue may respond with the formation of malignant neoplasms (liposarcomas) when a chemical carcinogen (3.4-benzpyrene), which is considered the chief cancerigenic agent contained in tar, is introduced into the subcutaneous tissue of guinea pigs and mice.

C. Traumatic Lipomas

In contrast to the very scanty evidence available regarding the causal role of specific agents, a nonspecific mechanical trauma to the fat tissue has been incriminated as the main or contributory factor in the production of these neoplasms. It is essential that in an evaluation of the claims advanced a sharp distinction is made between the solitary lipoma and the multiple symmetrical

lipoma, as the alleged traumatic causation of these two different types of lipomas affects different tissues, and involves a different action-mechanism.

a. Solitary Lipomas

A lipoma is a circumscribed, often lobulated, mass of fat cells usually surrounded by a relatively delicate fibrous capsule forming septa, which enclose the individual lobules. One or several vessels enter the mass and divide into an arborescent network. In many instances lipomas have a marked fibrous component (fibrolipomas). The appearance of a lipoma at the site of a previous single acute trauma has been reported by various observers. Grosch collected 36 cases of lipoma of the head, three of which developed after an injury. In an analysis of the histories of 28 cases of lipoma, Würz found that only one of these neoplasms was suspected of a traumatic genesis. This tumor appeared in the buttocks of a woman following a fall upon the side of the pelvis. Bosse-Lieschke noted that several scrotal lipomas appeared after a contusion of the scrotum. Graef collected a total of 62 cases of alleged traumatic lipomas from the literature. In a discussion of the causative factors of lingual lipomas, Smith cited Guelliot to the effect that trauma played a determining role in the growth of lipomas of the tongue in the opinion of this investigator. This contention is supported to a certain extent in that the great majority of these blastomas are located in the edges of the tongue, where traumatization by bites occurs most often [22 out of 40 lingual lipomas situated in edge of tongue (Smith)]. In the great majority of lipomas no causal relations to trauma exist, and the sequence of events recorded for numerous lipomas of alleged traumatic genesis makes such a causation highly improbable or impossible. The relative rarity of lipomas of the hands and soles, which are subjected to trauma upon many occasions, militates against the assumption of a frequent traumatic etiology. While the predominance of lipomas among females may be regarded as evidence supporting this viewpoint, it may be used against it by arguing that the female sex exhibits normally a more marked growth of fat tissue, and may possess for this reason a higher reactivity of this tissue to traumatic influences favoring neoplastic formations from regenerative proliferations of fat cells.

It is because of these considerations that the question of a relationship between trauma and the etiology of lipomas has remained a controversial one. The attitude of Knox in this respect is frankly sceptical, as this investigator points out, with some degree of justification, that traumatic lipophagic granulomas and cysts (Oehlecker) have been mistaken in earlier years for traumatic lipomas. A similarly negative opinion in this matter is held by Stern; Adair, Pack and Farrior.

Ewing does not share this conception, as he concedes that "trauma of many types has seemed to act as an exciting factor with many solitary superficial lipomas in subjects in whom a local or general predisposition must be as-

sumed to exist." This contention is supported by several observations. Trauma disarranges pre-existing blood vessels and may permit, through the subsequent new formation of capillaries, the regenerative growth of separate fat cells, which ultimately may assume an independent, neoplastic character. Such conditions are most likely to exist where a repeated, chronic trauma of fat tissue is operative. Such a mechanism is present and etiologically active in the production of certain peculiar types of lipomas, which involve the traumatic herniations of joint capsules and fascias, permitting the protrusion of fat lobules through these ruptures. The circulatory disturbances present and frequent traumatization sustained by the lobules stimulate the proliferation of fat cells, leading ultimately to neoplastic conditions. Lipomas of this genesis may be found in connection with injuries to joints (lipoma arborescens) (Ewing; and Madier) and associated with old inguinal and ventral hernias. Continuous pressure of an occupational type is said to be responsible for the excessive evidence of lipomas on the shoulder among Negro porters in Africa (pressure lipoma) (Grosch; Surmont and Sava; and Graef). Wolff reported lipomas of the shoulder following repeated contusions of this joint, and claimed a causal relationship between these episodes and the genesis of the lipomas. Similar considerations apply to the lipomas observed on the hand and fingers of manual laborers, of which Steinheil collected 49 cases from the literature (Lubarsch; and Schwarz). The sex distribution in this series is reversed in comparison to the ratio usually found in this respect. There were 23 lipomas in men and 14 in women.

Direct (hemorrhage and cellular necrosis) and indirect traumatic effects (congestion and traction upon fat lobules) thus may furnish the basis of an active proliferation of fat cells, which may assume ultimately a neoplastic character. The pre-conditions are supplied thereby for a malignant growth of fat cells (liposarcoma) as the result of a traumatic injury. Barnard reported the occurrence of a liposarcoma of the shoulder after repeated dislocations, and stated that the injuries accompanying these events had contributed to the causation of the periosteal liposarcoma. Ewing as well as Pack noted that some liposarcomas are caused unquestionably by a single, acute, crushing injury involving fat tissue. Both investigators agree that the adult type of liposarcoma with opaque, granular, spindle-shaped cells seems to follow trauma, while the embryonal variety of liposarcoma (myxoliposarcoma), commonly found in the groin, is of embryonal origin and has never been recorded as a sequela to trauma. Seids and McGinnis asserted that trauma in this respect is of doubtful etiological significance and blamed too often for the production of liposarcomas. It is conceded that liposarcomas have followed injuries and have developed from lipomas of long standing.

In connection with the alleged production of malignant lipomatous tumors, originating from traumatically destroyed fat tissue, it is important to refer briefly to some experimental attempts which have been made to elicit neo-

plastic responses by the injection of various types of fats, oils, and fat constituents. Andervont injected lard repeatedly and subcutaneously into 190 mice without obtaining any neoplastic reactions within 189 days. The subcutaneous injection of sunflower oil into 16 mice proved to be equally unsuccessful after six and a half months (Schabad). Repeated weekly injections of 1 cc. of lard, olive oil, pig's fat, oleic acid, linseed oil, cod liver oil, wheat germ oil, triolein, and myristic acid, respectively, into mice did not result in any neoplastic manifestations (Burrows, Hieger, and Kennaway).

The subcutaneous injection of lard or olive oil into 193 rats was followed by spindle-cell sarcomas at the site of injection in 8 rats. In one of these positive cases the injection of lard had been combined with the introduction of theelin, while in a second positive rat the olive oil injected contained arsenious acid. The intraperitoneal introduction of lard and olive oil, respectively, into mice and rats resulted (in one out of 60 rats and in two out of 248 mice) in the development of lymphosarcomatosis. These observations suggest, that, at least in rats and mice, the artificial introduction of processed fatty substances may cause blastomatous reactions.

b. Multiple Symmetrical Lipomatosis

The multiplicity as well as the widespread and symmetrical distribution of neoplastic lesions existing with multiple symmetrical lipomatosis precludes the possibility that the alleged traumatic cause may elicit such a response by a direct action upon the fat tissue. Ewing; Knox; and Stewart deny that trauma can be connected in any way with the production of these tumors. Kaufmann contended that the preexisting, symptomless lipomas are made painful by the trauma and thereby attract attention. Spitzmüller recently recorded ten cases of symmetrical lipomatosis, none of them showing any definite relation to trauma. The majority of these cases, however, were not cases with multiple symmetrical lipomas, but represented local bilateral accumulations of fat tissue in the region of the neck (so-called Madelung's Fetthals).

There exists a certain amount of reliable and suggestive evidence connecting the occurrence of multiple symmetrical lipomatosis with neurogenic disturbances caused by a previous traumatic injury to the spinal cord. Cases illustrating such a relationship were reported by Buschke and Casper; Buschke and Mattissohn; Buchterkirch and Bumke; Koch; Marimon; and Frank. The trauma usually incriminated was a fall causing a contusion of the spine or a vertebral fracture with secondary motor and sensory nervous disturbances. In some cases palpable nodes were noticed 6 to 8 days after the accident (Buchterkirch and Bumke; and Buschke and Casper), while in other cases the first tumors appeared more than a year after the injury (Marimon; Buschke and Mattissohn; and Koch). The lipomas did not develop all at one time, but increased in number gradually or in the form of several successive showers. Their appearance was often accompanied by neuralgic pains. It was not uncommon

that their distribution followed the same scheme as observed in multiple neurofibromas. In traumatic cases men only were involved. Trauma is not the sole and probably not the most frequent cause of multiple symmetrical lipomatosis, but other factors of endogenous or exogenous nature may produce those changes in the central nervous system, which are apparently essential for bringing about the trophoneurotic lesions in the peripheral tissue (Askanazy; and Kleissel). This conclusion rests not only on clinical, but also on experimental evidence. Experimental data cited by Löwy and Zondek indicate that nervous influences control the deposition of fat tissue on the basis of trophoneurotic influences. These investigators noted that a unilateral, hemiplegic adipositas of the leg could be produced in dogs and rabbits when the corresponding ischiatic nerve was injured by squeezing (Mansfeld and Müller; and Lostat and Vitry).

From the evidence presented it may be concluded that, unless the peculiar trophoneurotic response of the fat tissue upon an injury of the spinal cord is dependent upon some hitherto unknown, highly restricted, localized destruction of nerve tissue, additional contributory factors of a constitutional nature represent a prerequisite for a traumatic genesis of multiple, symmetrical lipomatosis. This consideration does not distract from the fact that a trauma may play an important causal role in the production of this unusual disease.

c. Traumatic Lipophagic Granulomas

In the discussion of the alleged causal interrelations between trauma and lipoma formation, attention was called to the fact that part of the evidence used in support of such a relationship dated from a time when the frequency and nature of traumatic fat necrosis and regeneration were not yet well understood. In recent years this condition has obtained increased importance, not so much as a disease which may be mistaken for true lipoma, but as a disorder of the subcutaneous tissue, especially when located in the region of the breast, which mimics the symptoms elicited by malignant tumors (carcinoma and sarcoma). Diagnostic mistakes of this type have been made repeatedly and have been the cause of incorrect therapeutic procedures (Livingston and Lederer; Bartsch; Lee and Adair; Dunphy; and Hadfield). Bartsch stated that in 17 out of 72 cases of traumatic, lipophagic granuloma of the breast a diagnosis of mammary cancer had been made.

The causative factors responsible for traumatic fat necrosis may be of mechanical, physical, or chemical nature involving the subcutaneous fat tissue (blows, x-rays, diathermy, radon implants, prolonged application of ice bag, and therapeutic injections of fluid into subcutaneous fat tissue) (Bartsch; Lee and Adair; Hadfield; and Oehlecker). In view of the relative rarity of such a response, it appears likely, however, that additional factors, possibly of intrinsic character, are essential for developments of this type (Neal and Ellis).

The most frequent location of lipophagic granuloma is the female breast

(Lee and Adair; Hadfield; Dunphy; Bartsch; Livingston and Lederer; and Haagensen), a fact, which accounts for the predominance of women affected by it. It has been observed occasionally in male breasts [two out of 72 cases (Bartsch)], as well as in extramammary sites [buttocks, especially around the anus; legs; arms; abdominal wall; and other parts of the body exposed to occupational trauma (Bartsch; Bartsch and Pollack; Shattock; and Lang)]. An abundant amount of fat tissue, such as present in large and full breasts, seems to predispose to the development of this traumatic lesion (Bartsch; and Lee and Adair). The average age occurrence is 50 years (Hadfield) (in 12 per cent of the cases the individuals affected were under 40 years and the youngest person recorded was 19 years old). The time interval between the traumatic event and the development of the tumor-like formation in the fat tissue varies from 3 weeks to 10 years (Lee and Adair).

Corresponding with the developmental type and phase, which were observed by the different investigators, the following names were given to this traumatic response of the fat tissue: traumatic fat necrosis, traumatic fat cyst, subcutaneous fat fission, oleogranuloma, subcutaneous lipogranulomatosis, and lipophagic granuloma. The lesion starts as an area of traumatized and necrotic fat tissue undergoing a quiet and painless autolysis or heterolysis, and forming ill defined cystic foci filled with fluid fat. Such a reactive area may grow rapidly in size by the participation of the surrounding tissue in the process of limitation and organization of the degenerating and necrotic tissue and its disintegration products. At the same time the deposition of calcium salts in the necrotic material produces a more or less marked induration of the primarily rather soft and fluctuating lesion. A lipophagic granuloma during a more advanced stage may present itself as one or several firm and sometimes partly fluctuating nodes of varying size. The induration is usually painless or only slightly tender. While it is movable in many instances, it is found to be adherent frequently to the skin (50 per cent) or to the deeper structures [10 per cent (Hadfield)]. These adhesions to the skin may give rise in the breast to a retracted nipple (10 per cent), and to the development of a typical "peau d'orange," such as is characteristic for mammary carcinoma. In addition to these two symptoms Lee and Adair noted that the following manifestations suggested, in some instances of lipophagic granuloma of the breast, a malignant condition of this organ: age of the individual, lack of pain, hard consistency, and adhesions to the deeper structures. These granulomas may simulate grossly in some cases a malignant neoplasia of the breast, as they appear as firm, opaque, non-encapsulated, greyish-white areas with yellow to brownish spotting, containing small cysts with a creamy content. Their outlines are irregular and fine, chalky white fascicles which extend from the central, white, hard, homogeneous mass and radiate in all directions. The brownish areas sometimes represent a xanthomatous degeneration of fat tissue which offers histologically certain great difficulties in its distinction from a xanthomatous degeneration of

mammary cancer (Haagensen). Some granulomas contain smaller or larger stony, calcified areas; others exhibit cysts with an oily content, which in turn are often predecessors of multiple cavities filled with calcareous material, merging ultimately into a single, solid calcareous mass.

The diagnosis of lipophagic granuloma depends sometimes entirely on the outcome of the histological examination of the tissue. Abrikosoff distinguished between the following five histological types of reactions of fat tissue, representing the end results of a traumatic fat necrosis:

1. Resorption of the fat released from the necrotic cells, and transformation of the granulation tissue into a tubercle-like conglomerate.
2. Resorption of the fat under formation of a cyst.
3. Resorption of the fat followed by the collapse of a cyst primarily formed, and the development of a scar.
4. Focal calcification of the fat tissue with encapsulation.
5. Total calcification or petrification of the necrotic fat tissue with encapsulation.

The histological examination of a lipophagic granuloma presents a cellular granulation tissue which consists, during the early stages, of a dense accumulation of fibroblasts and phagocytic cells in the marginal portion of the fat tissue necrosis, the phagocytes being engaged in the absorption of fatty acids. During a more advanced stage the indurated area is composed of lymphocytes, polymorphonuclear leucocytes, fibroblasts, innumerable phagocytic cells containing fat droplets, pseudoxanthoma cells filled with lipoid matter, and multinucleated giant cells (Haagensen; and Bartsch). There are deposits of druses of calcium soap and hemosiderin scattered throughout this tissue. Cholesterol crystals embedded in the tissue are often found surrounded by giant cells (Lang); similar cells may be seen in the neighborhood of foci of necrotic or structureless fat tissue, scattered through normal fat tissue. There are, moreover, productive inflammatory changes present in the blood vessels (obliterative endarteritis). Malignant transformations have not been noted in the cases observed so far.

d. Xantheloids

The presence of lipoids within the cytoplasm is not a characteristic feature of any definite type of cell, but may be found in a great variety of cells and under markedly differing conditions. A high lipoid content produces a foamy appearance of the cytoplasm. Cells showing such changes are called "xanthoma cells." The accumulation of lipoids in the cytoplasm of tumor cells is frequently an expression of a degenerative xanthomatoid transformation, which has been observed in a great number of different types of tumors [sarcomas, endotheliomas, fibromas, and carcinomas of different organs (kidney and breast) (Kirch; Lobeck; Wustmann; Kinoshita; and Haagensen)], or may be the result of a specific functional activity (hypernephromas). Such changes have no relation to any occupational activity or any occupational trauma.

Occupational trauma has been incriminated in the localization and distribution of xanthomatous deposits of mesenchymatous cells of metabolic and constitutional etiology, and in the production of mesenchymatous granulomas composed of xanthoma cells (xanthosarcomas or xanthogranulomas). Among the constitutional metabolic lipoidoses [hypercholesteremia in diabetes, with formation of local lipoid infiltrations of the subcutaneous tissue (xanthomas), Schüller-Christian's disease, Niemann-Pick's disease, Gaucher's disease, and Tay-Sachs' amaurotic idiocy] the localization of diabetic xanthomas, preferably at sites (elbow, knee, and knuckles) subject to trauma, sometimes shows an occupational relation (Sugg and Stetson; Michelson and Laymon; Schmidt; and Beeson and Albrecht). Trauma has no part in the causation of these diseases (with the possible exception of diabetes), some of which display a more or less definite predisposition to members of the Jewish racial mixture (Chester and Kugel).

It is argued that a local trauma may cause the formation of xanthomas, through an intracellular infiltration of mesenchymatous cells with cholesterin and cholesterin esters, by setting off or completing the local disintegration of the emulsion of the various fatty constituents present in the blood and tissues which is apt to occur in the presence of a lipemia. The xanthomas seen in diabetics are yellow to orange brown, firm to soft papules, and plaques or tuberous nodules. They are usually multiple and consist of large polyblastic cells with a foamy cytoplasm and a round to oval eccentric nucleus. The lipoids present in the cells are anisotropic and show, upon examination with polarized light, spherite crosses which disappear upon warming and reappear upon cooling. The lipoid is stained a dull brown to orange red with sudan III and dark blue to blue purple with nile blue sulfate. Crystalline inclusions and granules within the cells are not stained.

Experimental studies have confirmed the localizing role which trauma plays in the development of xanthomas. Anitschkow produced xanthomas in rabbits, which had been made hypercholesteremic by an oral administration of cholesterol at sites traumatized by the injection of turpentine oil and celloidin. Similar results were obtained in rabbits by Schaaf, who fed cholesterol to these animals and obtained xanthomas on the neck after mechanical traumatization. Borst observed the development of xanthomatous nodules around perforations caused by the identification marks in the ears of rabbits fed with cholesterol. Observations made by Rusch, Baumann, and Kline indicate that physiological trauma may be active in the localization of experimental xanthomas. These investigators noted the development of xanthomatous nodules in the footpads and in the regions of the knees of rabbits fed for many months with cholesterol.

Xanthogranulomas, also called xanthosarcomas, are cellular granulomas consisting to a large degree of polyblastic xanthoma cells. They are found in places exposed to chronic trauma (such as tendon sheaths, synovia of joints,

and bursae of hands and arms). Repeated external trauma (Biebl; Sauerbruch; Winkler; and Dietrich) and a single, acute trauma may lead to the development of an inflammatory, resorptive xanthogranuloma (knee joint) (Kisse; and Bonn). These yellow colored hyperplasias contain plaques of the large xanthoma cells with their honeycomb-like cytoplasm filled with fine lipoid droplets and granules. These cells often form sheaths around blood vessels. There are in addition strands of fibroblasts and multinucleated giant cells of the foreign body (nuclei arranged in a wreath) and the Touton type (nuclei placed radially in the longitudinal axis and surrounded by a fringe of granules). The foam cells sometimes show loss of cell contours, which results in a merging of the cellular clumps into a larger lipoid mass containing cholesterol crystals and leaving the typical slit-like defects in the tissue following its extraction with alcohol. Hyalinization of the connective tissue strands and of the walls of the blood vessels as well as small lymphocytic infiltrations are often observed. The xanthosarcomas are usually local lesions, which do not recur after removal, grow expansively, and do not produce metastases (Oberndorfer). Occasionally infiltrative growth and secondary deposits are noted, indicating the transition from a state of inflammatory hyperplasia into that of a neoplastic hyperplasia (Pack).

6. JOINT CAPSULES AND TENDON SHEATHS

Capsules of joints and sheaths of tendons form the walls of cavities into which these membranes secrete a sero-mucinoid liquid. They consist of a fibrous, outer layer and a loose, inner, synovial layer, composed of fibroblasts embedded in an edematous matrix containing a few fat cells and blood and lymph vessels. Accidental and occupational trauma acting on these tissues may give rise to several types of pseudotumors.

A. Ganglions of Tendon Sheaths

Ganglions are cystic formations filled with a clear, viscous material, found most frequently on the dorsal aspect of the wrist and less often on the dorsum of the knee, ankle, foot, and palmar surface of the wrist. They represent pseudotumors of the tendon sheaths most commonly observed in people who have a constant occupational motion of the wrist, hands, or feet, such as typists, pianists, and washerwomen. They rarely follow a single, acute accidental trauma (injury or strain) to the tendon sheaths (Brunschwig; Bearse; Payr; and Gross). Their etiologic relation to chronic occupational trauma is supported by the fact that there exists a likelihood of repeated ganglion formation for persons affected by this condition, unless any further strain and chronic abuse of the tendon sheaths is eliminated by a change of occupation.

The pathogenesis of these cysts is still controversial. Some investigators maintain that they are the result of a herniation of the synovial membrane

through a rent in the fibrous sheath. Others contend that they represent the product of a mucinous degeneration in a fibroplastically thickened part of a tendon sheath (Payr; and Brunschwig). Unilocular and multilocular cysts are formed by the coalescence of various foci of colloidal disintegration. The walls of the cysts contain a myxomatous tissue, while the lining and villous formations, found in larger spaces, resemble structures present in the normal synovia. The thick fibrous walls of old ganglions may contain calcareous incrustations and papillary projections or cartilagenous excrescences. Giant cells are found in the tissue composing such formations.

B. Intraarticular, Synovial "Osteochondromas"

Chronic traumatic inflammations of the capsule of joints may give rise to primary hyperplastic and secondary metaplastic changes in the synovial membrane, associated with alterations of the physico-chemical conditions in this tissue. Under the influence of these factors metaplastic synovial villi are transformed into chondromatous nodules, the centers of which may undergo calcification and ossification as long as these pedunculated or sessile, synovial nodules are provided with vascular connections by the synovial membrane. After the detachment of these nodules from the synovia and their appearance as free bodies in the articular cavity (osteochondromata), the bony structures become atrophic, while the cartilagenous coating remains alive as it receives nutrition by osmosis (Carnevali).

C. Xanthogranulomas (Xanthomas) of Tendon Sheaths and Articular Capsules

Trauma plays an etiological role in the development of some of the xanthomatous formations originating from the synovial membrane of joints and tendon sheaths (Willenegger). Xanthogranulomas, which represent the most frequent type of the relatively rare blastomatoid and blastomatous reactions of the synovial tissue, frequently follow a severe and direct trauma, such as a fall or a blow, to these tissues. In a series of 109 cases of xanthoma of synovial membranes collected by De Santo and Wilson from the literature, 25 of the 30 cases, in which data on a traumatic aspect were available, exhibited a connection of the onset of the clinical symptoms with a traumatic episode. De Santo and Wilson contended that the role which the injury played in these cases consisted merely of an aggravation of a preexisting condition by eliciting the first subjective symptoms. Their histological data, however, showed clear and definite evidence concerning the effect which the injury elicited in the synovia and the adjacent tissues, and indicated the causal role which it played in the production of the resulting xanthomatous granulomas.

Galloway, Broders, and Ghormley noted that occupational trauma assumes a larger part than most students of xanthoma are wont to believe in the production of xanthomas of the tendon sheaths and synovial membranes. In support

of their contention these investigators pointed out that these tumors are more frequent on the fingers and hands than on the forearms and arms, and on the feet and ankles than on the rest of the extremity. The trauma eliciting such xanthomatous responses may be mild, chronic, or constant and, therefore, may not be properly appreciated. A traumatic history was present in 44 per cent of their series of 70 cases, 39 of which were housewives, while the rest were clerks, farmers, and laborers, that is, persons exposed to every day trauma. These blastomatoid formations are found somewhat more frequently in men (59 per cent) than in women (41 per cent). The knee joint is the most often affected joint (36 out of 41 cases) (De Santo and Wilson). Persons between 20 to 40 years of age are generally the most affected.

The xanthomatoid granulomas are composed of the typical lipoid-containing foam cells, a fibroblastic stroma, numerous capillaries, multinucleated giant cells, and varying amounts of a brown to yellow, intracellular, and occasionally extracellular, hematogenous pigment. The adjacent synovial tissue usually exhibits changes, such as seen in chronic hemorrhagic villous synovitis. Malignant transformations have not been observed.

D. Synoviomas

There exists a certain amount of clinical, circumstantial evidence connecting the formation of malignant synoviomas of the joint capsules and tendon sheaths with an antecedent trauma. Pack noted that a history of trauma which seemed to be authentic and adequate was related in almost every case of this type of neoplasm. Pack contended that the traumatic hemorrhage in connection with the reparatory processes, following the laceration of tendon sheaths and joint capsules, provides the essential basis for a progressive proliferation, resulting in true synovial tumors, usually of a malignant type. Illustrative cases of this kind of traumatic neoplasia were reported by Chiurco; and Schwarz.

7. OSSEOUS AND CARTILAGENOUS TISSUES

A. Chemical Agents

Occupational neoplasms of the bone or cartilage caused by an industrial exposure to chemical agents, with the exception of the radioactive substances, are not on record. While there exist occupational contacts with certain chemicals (lead, fluorine, and phosphorus) which produce specific bony lesions, none of these result in the production of benign or malignant proliferative manifestations. They do cause changes in the chemical composition and structure of the bone (lead and fluorine), or elicit necrotizing reactions in the bone (phosphorus).

Experimental studies of recent years have shown, on the other hand, that bony tissue is capable of responding with the production of osteogenic sarcomas upon direct contact with synthetic carcinogenic chemicals, such as occur

normally as constituents of tar. Brunschwig and Bissell succeeded in eliciting neoplastic reactions (osteosarcomas) in the tibia of a mouse through the injection of 3.4-benzpyrene into the medullary cavity of this bone, while a fibrosarcoma of the femur was obtained in a rat after the introduction of methylcholanthrene into the marrow cavity. In subsequent experiments these investigators placed small pellets of paraffin containing methylcholanthrene by osteotomy into the lower end of the femur of 33 rats, and observed 8 months later osteogenic sarcomas in four of these rats. There were no metastases from these tumors after 16 months. Rusch, Baumann, and Maisin obtained periosteal fibrosarcomas in the long bones of two rats, after the intramedullary injection of 1.2.5.6-dibenzanthracene.

B. Physical Agents

a. Ultraviolet Rays

Although it is not conceivable that ultraviolet rays can act directly upon the cartilaginous or bony tissues of man under any kind of occupational condition, and thus elicit neoplastic responses, experiments of Putschar and Holtz have shown that the different anatomical conditions present in mice permit a direct action of these rays upon the cartilaginous tissue contained in the ears of these animals. These investigators reported the production of chondrosarcomas in the ears of mice following a prolonged irradiation with ultraviolet rays, which caused a severe actinic dermatitis.

b. Radioactive Substances

I. PHYSICAL AND TECHNOLOGICAL ASPECTS

There exist three families of radioactive substances which emit one or more of the following three types of rays: alpha-rays, beta-rays, and gamma-rays.

Alpha-rays, which are given off by the majority of these substances, are positively charged helium atoms moving at a speed of 15,000 to 20,000 kilometers per second. They possess little penetrating power (2.5 to 8.6 cm. of air; and 0.06 mm. of aluminum), but exert an important and powerful biological effect.

Beta-rays are, like cathode rays, negative electrons. Their speed approaches that of light waves and varies from 100,000 to 300,000 kilometers per second. Beta-rays have a higher penetrating power than alpha-rays. Both types of rays are corpuscular.

Gamma-rays are non-corpuscular rays. They are similar to roentgen-rays and comparable to light rays, as they are electro-magnetic waves of varying wave lengths. The gamma-rays possess a marked penetrating power.

Through the loss of energy and substance caused by the emission of the corpuscular and electro-magnetic waves, the various radioactive substances are transformed into radioactive elements of a lower type, until they are finally

converted into non-radioactive lead. The time which elapses during each of these successive transformations varies greatly, from fractions of a second to thousands of years. The time which is needed by a radioactive element to give off half of its actinic energy by atomic disintegration is called the half-time of the particular substance, which is characteristic of the different radioactive elements. The members of the three radioactive series, the type of rays emitted by them, and their respective half-times are presented in the table on the following page, which shows at the same time the order in which the various disintegration products are formed.

The succession of various types of rays, emitted by the different kinds of disintegration products, is of significance for the proper understanding of the biologic effects produced by a radioactive substance which has entered the body and which is retained there for some time, or which remains as a deposit in certain tissues over a prolonged period. The elements of the uranium-radium series and thorium series as well as their various compounds possess industrial and medicinal importance. Those contained in the actinium series have so far mainly scientific interest, except when they occur as admixtures of the members of the radium series, as the actinium members are found in uranium pitchblende.

Uranium ores, which are mined on a commercial scale in Joachimsthal (Germany), Katanga (Congo), and Great Bear Lake (Canada), are pitchblende, autunite, camotite, betafite, and chalcolite containing various proportions of radium (2 mg. to 100 mg. per ton). For the extraction of the radioactive substances the minerals are crushed to a coarse powder. After repeated washings the powdered material is subjected to several chemical procedures, resulting in a concentration of the radium in the products obtained by an interaction of barium chloride with radium. When the product has become sufficiently rich in radioactive substances, it is transferred from the processing plant to the purification and crystallization laboratory, where the radium is separated from the barium by repeated fractionated crystallizations based on differences in solubility of the two substances, barium chloride being more soluble in water than radium chloride. By redissolving and recrystallizing the radium chloride precipitate in hot water, an increasingly pure radium product is obtained gradually. About a hundred such crystallizations, each one taking approximately a day, are necessary before a satisfactory end product is reached. In well-conducted laboratories all open treatments and heating processes are carried out under a hood with a forced draft. Ventilating fans are kept running during work and the windows are kept open as much as possible. During the final stages of the crystallization process the evaporation dishes are placed in thick lead shields, as the hazard increases with the concentration of the radioactive product. The active purified compound is placed into small glass tubes, which are sealed and kept in lead containers which provide the proper protective screening. The tubing of the active compounds is carried

RADIOACTIVE ELEMENTS

I. Uranium-Radium Series

Name of Element	Half-Time Value	Type of Rays	Atomic Weight
Uranium I	4.67×10^{9} Years	alpha	238.2
Uranium X_1	24.6 Days	beta-gamma	234
Uranium X_2	1.15 Minutes	beta-gamma	234
Uranium II	2×10^{6} Years	alpha	234
Uranium Y	25 Hours	beta	
Ionium	6.9×10^{4} Years	alpha	230
Radium	1690 Years	alpha-beta	225.97
Radon (Radium-emanation)	3.85 Days	alpha	222
Radium A	3 Minutes	alpha	218
Radium B	26.8 Minutes	beta-gamma	214
Radium C	19.5 Minutes	beta-gamma (alpha?)	214
Radium C_1	10^{-6} Seconds	alpha	214
Radium C_2	1.32 Minutes	beta	210
Radium D	16 Years	beta-gamma	210
Radium E	5 Days	beta-gamma	210
Radium F (Polonium)	136 Days	alpha	
Radium G (Radium-lead)	—	—	206
(ordinary lead)			207.2

II. Actinium Series

Name of Element	Half-Time Value	Type of Rays	Atomic Weight
Uranium Y	1.04 Days	beta	
Proactinium	1.2×10^{4} Years	alpha	approximately 230
Actinium	20 Years	(beta)	" 226
Radioactinium	19.5 Days	alpha-beta gamma	226
Actinium X	11.4 days	alpha	222
Actinon (Actinium-emanation)	3.92 Seconds	alpha	218
Actinium A	0.002 Seconds	alpha	214
Actinium B	36.1 Minutes	beta-gamma	210
Actinium C	2.15 Minutes	alpha-(beta)	210
Actinium C_1	0.005 Seconds	alpha	210
Actinium C_2	4.76 Minutes	beta-gamma	206
Actinium D (Actinium-lead)	—	—	206

III. Thorium Series

Name of Element	Half-Time Value	Type of Rays	Atomic Weight
Thorium	1.31×10^{10} Years	alpha	232.15
Mesothorium I	6.7 Years	(beta)	228
Mesothorium II	6.2 Hours	beta-gamma	228
Radiothorium	1.9 Years	alpha-beta	228
Thorium X	3.64 Days	alpha	224
Thoron (Thorium-emanation)	54.5 Seconds	alpha	220
Thorium A	0.14 Seconds	alpha	216
Thorium B	10.6 Hours	beta-gamma	212
Thorium C	60.8 Minutes	alpha-gamma	212
Thorium C_1	10^{-11} Seconds	alpha	212
Thorium C_2	3.1 Minutes	beta-gamma	208
Thorium D (Thorium-lead)	—	—	208

out in a glass case with a door just large enough to admit the hands of the operator. The crucible containing the active compounds and the tube are held in special holders (Morris; and Laborde and Leclercq).

Mesothorium, which has chemical qualities similar to radium, is obtained chiefly from thorium ores with methods corresponding to those used in the production of radium. The mother substance is monazite sand mined in Brazil, and contains about 5 per cent thorium oxide. This content of mesothorium is equivalent in radioactivity to 2 mg. of radium per 1000 kg. of monazite sand. For the recovery of the mesothorium the sand is first heated for a long time together with sulfuric acid and some barium salt. With the addition of water the mesothorium and its admixture of radium precipitate out of solution together with barium sulfate and other impurities, while thorium and other rare earths remain in solution. The precipitate is then treated like that obtained from radium ores, that is, it is boiled with soda and extracted with hydrochloric acid. The hydrochloride is crystallized numerous times for increased purification. The commercial mesothorium preparations contain about 25 per cent radium, which originates from the uranium present as a normal admixture of the monazite sand (Friedländer).

II. OCCUPATIONAL EXPOSURES

The miners and crushers of radioactive ores and the loaders of the powdered material are exposed to the inhalation of dust from radioactive ores and to gaseous radioactive substances given off by the ores as degradation products of radioactive elements. Minor amounts of radioactive dust may be ingested during these activities. The degree of hazard existing for the crushers and loaders is apparently relatively small, the radioactivity of the ores being low. So far occupational malignancies attributable to this source have not occurred among this group of workers at Joachimsthal.

A considerable degree of exposure may exist for the employees of the crystallization laboratories, as the substances handled here come in contact with the workers in the form of radioactive dust and give off gaseous disintegration products, radon and thoron, respectively, which escape into the air of the workrooms. While these emanations themselves emit only alpha-rays, their disintegration products produce alpha-, beta-, and gamma-rays. Whereas the inhaled radon is exhaled for the most part and cannot do much damage, thoron is rapidly transformed into highly active solids remaining in the body after the inhalation of thoron and its resorption into the blood.

In addition to the hazards connected with the production of the various radioactive substances for commercial and medicinal use, there exist appreciable degrees of exposure when these highly active products are employed for numerous industrial purposes and handled for therapeutic procedures. Thorium preparations (thorium nitrate) are extensively used for the impregnation of gas mantles in Auer lamps. Poisonings with radioactive thorium

compounds have occurred among employees of factories in which these mantles are made. Chronic intoxications by radium and mesothorium compounds have been observed among attendants of medical therapeutic radiological laboratories.

While fibrosing and atrophic lesions as well as neoplastic reactions of the skin, lung, and hematopoietic tissues have been observed as the result of such exposures, there was in no instance a malignant tumor of the bony or cartilaginous tissue present. Similar degenerative reactions have been found in persons who consumed radioactive water for therapeutic purposes (Gettler and Norris; and Fernan and Smerecker). Such effects are elicited only by naturally radioactive water containing radon, radium D, radium E, and polonium or by artificially radioactive water, that is, water to which small amounts of radioactive substances have been added. The radioactive substances present in such agents are stored and accumulated in the body. These substances are absent when the so-called "radioactivated" water is used, which comes from radium springs or is activated from emanators or other devices and contains the short-lived and readily excreted radioactive radon gas. The "radioactivated" water becomes inactive within a few weeks (Evans; Flinn; and Fernan and Smerecker).

Although the above-mentioned occupations with hazards from radioactive substances have remained, so far, free from industrially conditioned neoplasms of the bony and cartilaginous tissues, the occupational exposure to these agents existing in industries handling radioactive luminous paints has resulted in the production of such cancerous reactions among their employees. Cases of this type have been observed only in several American plants, in which brushes were used for the application of the luminous paint (Martland; Martland and Humphries; and Flinn). An inquiry conducted by the International Labour Office among European plants of this kind (Switzerland, France, Germany, England, and Belgium), where the paint is applied with a stylus, showed an absence of similar ill effects among the workers (Lacassagne; Duval, Regaud, Roulier, and Béclère).

The investigations of Stewart showed that in addition to the hazard connected with the manufacture of the luminous paint and its application on watch and clock dials, a dangerous exposure to luminous paint exists in other occupations in which this material is handled. Luminous paint is used for numerous types of military equipment, such as sighting lines of trench mortars, sighting instruments of artillery, instrument boards of airplanes and submarines, and small field compasses as well as on house numbers and push buttons. The hazard of exposure to radioactive material is more pronounced when water is used for the preparation of the paint, than when an oily adhesive is used, as the watery paint must be renewed more often than the oily one.

The removal and renewal of luminous paint is connected with a marked hazard, as the radioactive substance is still present in the paint when the zinc

oxide has lost its luminosity. The removal of the old paint entails a dust hazard (respiratory introduction and skin contact). Stewart pointed out that laboratory workers handling and manufacturing radioactive material were found to be less continuously exposed, as a rule, and better protected than the dial painters. Depending upon the type of contact with the radioactive substances (skin, inhalation, and ingestion), there occurred different types of manifestations from radium poisoning. There were, according to Stewart, in the 31 establishments handling radioactive substances and employing 253 workers in United States, 23 fatalities from radium poisoning and 19 still living individuals showing symptoms of this disease. The presence of radium poisoning was suspected moreover in 2 fatal and 6 living cases. The largest number of poisonings (33) was furnished by the luminous dial painting industry.

In appraising the relative hazard from radium poisoning in this industry, consideration must be given to the fact that many tasks in the manufacture of luminous dials do not entail an intimate contact with the radioactive material (Bloomfield and Knowles). Workers applying black paint, operating transfer presses, sewing hands on cards, trimming and wrapping dials, distributing dials for painting, and making gelatine pads have only a minor degree of exposure. Tasks which are associated with a close contact with radioactive material are painting of dials with luminous material, mixing of the paint, dusting of the dials, operating the radium transfer press, weighing radioactive material, painting, shipping, repairing, and inspecting radium work, and instructing in the performance of these duties. A second serious health hazard, complicating and possibly aggravating the effects produced by the radioactive substances, may be introduced into such operations by the use of organic solvents, such as benzol, for the cleaning of the applicators, as substances of this type affect the hematopoietic tissues in a similar way as the radioactive material.

Schwartz, Knowles, Britten and Thompson, who made comprehensive studies on the degree of radioactive hazard existing for the various types of workers employed in the luminous dial plants in United States, made the following observations:

Dust in the general air of the workroom was found to be radioactive (an average of 9.8×10^{-10} grams per 10 cubic meters of air). In the vicinity of dial painters the radioactive content of aerial dust was from two to three times that found in the general air. Near dusters it was many times as high. The air of workrooms when freed from dust showed the presence of radon in amounts averaging 2000 times that of normal air. Workers were found to be exposed to gamma and beta rays. The average gamma ray exposure of the workers was equivalent to that which would be produced by about 1 mgm. of radium 50 cm. from the worker. There were no skin necroses of the fingers of the workers indicating a direct radiation effect. An accumulation of radioactive material was noted in the bodies of workers who handled or had previously handled

radioactive material. The amount present was related to the length of exposure. The greatest amount of radium found in an individual of the occupied group was 3.5 micrograms, while that of an individual of the formerly occupied group was 11.3 micrograms. Although the use of mesothorium in the paint had been discontinued since 1927, there was still a continuing rate of accumulation of radioactive material among the workers of the occupied group, and there existed still an appreciable amount of mesothorium in the bodies of the workers of the formerly occupied group. The average erythrocyte count was lower than normal in members of both groups, while only members of the formerly occupied group showed upon roentgen-examination focal atrophy or osteoporosis as well as densifications of the jaws.

III. HISTORICAL ASPECTS

The use of luminous paints on watch dials was first introduced in Germany in 1908. In 1923 the attention of the United States Radium Corporation was called to the possible existence of an industrial hazard in its plant located at Orange, New Jersey, by a dentist, who had observed several cases of necrosis of the jaw among employees of this establishment (Castle, Drinker and Drinker; and Flinn). Two years later Martland, Conlon and Knef reported severe leukopenia and anemia among girls employed in this plant in which luminous paint was applied to watch dials. Investigations instituted afterwards brought out the following facts:

From 1917 to 1924 an accumulative total of approximately 800 girls were employed in this factory, which was engaged in the painting of dials on clocks and watches with a luminous paint. The number of girls working at any one time varied between 12 to more than 200. Some of the girls were employed in this work 6 to 9 years, many for shorter periods. The paint used consisted of crystalline, phosphorescent zinc pyrosulphide, rendered luminous by the addition of small amounts of sulphate salts of radium, mesothorium, and radiothorium (highest amount 1 mgm. radium element or its equivalent mixed with 8 gms. of zinc sulphide, usually, however, with 30 to 40 gms. of this chemical). Some of the girls employed were engaged in the preparation of the paint by mixing the powdered chemical with an adhesive compound in a small crucible with the aid of a glass rod and thinning the paint with distilled water to the required consistency. When this operation was done energetically radioactive material was spilled on fingers, clothing, benches, and floors. The girls transferred the radioactive material later from their hands to other parts of their body (face and hair), which became luminous when "flashed" and then examined in a dark room. The aprons of these girls shone even after return from the laundry as if the paint had been set in the washing process. There was, on the other hand, no luminosity of those parts of the body where an active contact of the skin with the paint had not taken place. The paint could be washed off readily from the skin with soap and water.

Other girls applied the ready made paint with camel's hair brushes to the dials. After each application of the paint the brush was dipped into water and then wiped clean with a cloth. It was customary with the girls to point the brush, after dipping it into the water, by drawing it between the lips. Thus, some of the paint which was stripped off during this procedure remained attached to the lips and was later ingested. In some operations the radioactive material was dusted on the dials after these had been provided with a coat of enamel or of zinc sulphide with varnish. The finely powdered, radioactive luminous composition was dusted on before the coating had dried completely. The excess material was removed later with a brush. A fine dust was found to settle on the hands of the operators, who inhaled some of the radioactive matter.

There had been 15 fatalities among girls employed in this plant during this period. Five of them had died with symptoms suggesting the presence of an occupational poisoning with radioactive substances. These girls developed some time before death a necrosis of the jaw resulting in loss of teeth and resembling to some extent the type of necrosis of the jaw seen in phosphorus poisoning. There had been no appreciable or characteristic changes of the blood in the exposed girls at this time (1926).

Flinn, who investigated the allegedly occupational character of these disease conditions which had been brought up in connection with the painting of luminous dials, pointed out in refutation of such claims that: 1. the death of five girls from a disease of unknown cause was statistically insignificant; 2. that the medical examination of two-thirds of the girls employed at dial painting at that time in United States, and a study of similar workers in England and on the European continent, where a total of 4,000 to 5,000 girls had been employed in this industry, had not revealed a single additional case of necrosis of the jaw outside of Orange, where 50 per cent of the workers had teeth extracted since beginning work in that industry; 3. that the study of the blood of the workers did not reveal any constant or marked changes related to the duration of exposure (14.2 per cent of the workers had a mononucleosis above 8 per cent); 4. that the radium necrosis observed after therapeutic applications of radium to bony tissues exhibited first a porosity, which developed gradually after months or even years following the exposure and which ended in a complete disintegration and sequestration of the bone, while the bone necroses present in the dial painters displayed a gelatinous liquefaction of the jaw bone during the later stages of the disease; 5. that a phosphorus etiology of these changes could be dismissed as the phosphorus necrosis of the jaw is characterized by the multiplicity of the porotic areas, which appear to be well isolated from each other; and 6. that feeding experiments conducted on animals had shown that 98 per cent of the ingested radioactive material was excreted within a few days after the exposure was stopped. The application of the paint to the skin and oral mucosa of goats and guinea pigs, continued for over six

months, did not result in any local irritation or changes of the jaw nor in an irritation of the gastro-intestinal tract.

In spite of these numerous arguments advanced by Flinn against the possibility of an occupational origin of the bony lesions observed, he had to reverse his opinion and concede this fact, when one year later two cases of jaw necrosis were observed among girls employed in a luminous dial plant in Connecticut. While the electroscopic examination of the bodies and respiratory air of the workers of the Orange plant had been negative as to radioactivity, one of the cases from Connecticut showed radon in the respiratory air. There existed a profound anemia (35 per cent hemoglobin; 3,100,000 erythrocytes; and 6,100 leucocytes) and a fracture of the femur following a fall. Similar symptoms were exhibited by the second case found in the Connecticut plant.

Any doubt concerning the occupational origin of these conditions, which may have lingered on, was dispelled definitely and thoroughly by the evidence presented and the analyses made by Martland in 1929, and by the investigative survey conducted by Stewart (1929) under the direction of the United States Department of Labor. The observations made and conclusions reached by these investigators were confirmed and extended by Schwartz, Knowles, Britten, and Thompson (1933), who examined by order of the Surgeon-General the present and former workers employed in the seven dial painting factories, employing 14 men and 228 women, located in the United States.

IV. INCIDENCE

While some of the workers in the luminous dial plants succumbed early to the effects of a refractory, incurable, leukopenic anemia or septicemia ensuing from the necrosis of the jaw (death usually occurred in these cases during the first four to six years after cessation of exposure), others escaped these sequelae for a period of six to seven years and developed, after an intervening period of apparent good health usually accompanied by a milder type of regenerative anemia, crippling bone lesions of the type of radiation osteitis, which ultimately were transformed into malignant osteogenic sarcomas. These neoplasms caused the death of two dial painters from 1924 to 1927. Three additional cases were observed during the following years (up to 1930) (Martland) and two new cases were reported in 1934 (Flinn), so that there are at present seven cases of osteogenic radium sarcoma on record, representing approximately 30 per cent of the total number of fatalities from radium injury found among this group of workers. It may be mentioned that there exist four additional cases in which an osteogenic malignancy was suspected. The neoplasms occurred in female workers in all instances.

V. SYMPTOMATOLOGY

The ingestion and inhalation of radioactive substances as well as the exposure to penetrating external radiation present in workers of the American

luminous dial plants caused serious hematic disturbances (severe anemia of the pernicious type) and destructive changes in the bones, especially the jaws. The osteogenic lesions were particularly frequent in bones subjected to physiological strain and trauma (jaws, scaphoid, vertebrae, and head of femur) (Martland). The subjective symptoms elicited by these bony alterations consisted of swelling of the affected region, pains in such areas, especially at night, neuralgic pains, gradually increasing size of the diseased bone producing disfiguration (orbital bulging of eye), spontaneous fractures with delayed callus formation, interference with the motion (limping), and other crippling effects (obliteration of vagina by growth of the pelvic bones) caused by the osteitis deformans. The osteolytic processes found in the jaws resulted, because of their relation to the tooth structures and proximity to the oral mucosa, in infectious complications which led to extensive and intractable necrosis of the mandible and maxilla. Roentgen-examinations of the bones showed evidence of a radiation osteitis of a mixed osteolytic and osteoblastic type (spotty rarefaction and densification in multiple areas of many bones). The bones of the skull exhibited a moth-eaten osteoporotic appearance. Malignant bony lesions of osteolytic or osteoblastic type were primarily multifocal, while metastases of these osteogenic neoplasms into other bones were absent. The tumors grew rapidly after once being established and spread by way of the blood vessels. While in the differential diagnosis at the various stages of the disease, conditions such as chronic osteomyelitis, phosphorous necrosis, and tuberculosis of the bones and osteogenic sarcoma of unknown etiology, had to be considered, the true character and causation of these osseous lesions became evident and conclusive with the history of the occupational contact with radioactive substances, and the demonstration of radioactivity of the body of the affected individuals.

VI. LOCATION OF THE NEOPLASMS

Whereas the radiation osteitis occurring under these conditions attacked the bones exposed to stress and weight (head of femur, acetabulum, and scaphoid), osteogenic malignancies did not follow invariably this pattern, as they were located in the distal end and trochanter of the femur, scapula, vertebrae, orbital bone, ileum, ethmoid, and calvarium. Primary multiplicity in several bones existed in three of the five cases reported by Martland. The time of occupational exposure to radioactive material varied from one to more than four years.

VII. AGE

The age of the dial painters suffering from osteogenic sarcoma was relatively young, as the latency period for these tumors is rather short compared with that of other occupational cancers. The following data covering the five cases reported by Martland illustrate this point: the respective ages at autopsy were 20, 33, 34, 27, and 30 years. The ages of the four suspected cases of

osteogenic radium sarcoma were 30, 27, 23, and 32 years, respectively. The evidence indicates that time, type, and intensity of exposure seem to determine largely the age of onset of this occupational neoplasm. A predisposing factor of the nature of physiological tissue senescence is obviously absent in the production of these tumors.

VIII. CAUSATIVE MECHANISM

Under the working conditions observed at the luminous dial plants, radioactive material gained access to the body by way of the respiratory and alimentary tracts. Radioactive material in the form of dust or gaseous substances (radon and thoron) may enter the lung, where the gaseous products inhaled are in part precipitated as solid degradation products on the surfaces of the lung, from where they may in association with the dust particles either act directly upon the pulmonary tissue or enter the blood stream and become deposited in remote parts of the organism. The amounts of radioactive substances introduced by the respiratory route are of minor importance (Barker) when compared with the quantities ingested daily by the painters, because of their habit of pointing the brushes contaminated with the luminous paint by drawing them between their lips. Although the greater part of the ingested radioactive paint is rapidly eliminated with the feces, small portions pass through the gastro-intestinal mucosa and are distributed in the body by way of the lymph and blood. The radioactive substances are retained in various phagocytic elements [vascular endothelium, reticulo-endothelium (liver, spleen, lymph nodes, follicles of appendix, thymus, and bone marrow), histiocytes, and pericanalicular cells of testis], in the liver cells, cells of the reticular zone of the suprarenal, and particularly and most intensively in the bones, where they accumulate mainly in the outer portion of the cortex, replacing calcium and being probably deposited as phosphates (Flinn). While all bones become thus involved, the radioactive material is not distributed in them uniformly, but occurs in the individual bones in scattered patches. The radioactive substances are held in the bones for a more prolonged period than in the cells of the reticulo-endothelial system, as they were present in the bones of individuals dying from three to eight years after cessation of work, but were not demonstrable in any other organ. The radioactive substances penetrate the placental filter of a radioactive mother and may be transferred to the fetus (Martland; and Flinn).

Whereas the biological action exerted by the radioactive substances deposited in the various organs may be of a mechanical nature (blockade of phagocytic cells), a chemical character (metallic effect), or a physical type (actinic energy), it is the last mentioned mechanism which is most important and most powerful in eliciting the biologic reactions observed. Through the investigations of Martland it was demonstrated that individuals with fatal radium poisoning had from 10 to 180 micrograms of radium, according to the electrometric method, in their bones, emitting penetrating rays which consisted to

92 per cent of alpha-rays and to 8 per cent of beta- and gamma-rays. Martland expressed the opinion that the main and most marked biological effect is exerted by the alpha-rays, while the more penetrating beta- and gamma-rays play a minor role in this respect.

This conclusion of Martland was based upon the following arguments: as the mass of an alpha particle is 7,000 times larger than that of an electron, the kinetic energy of an alpha particle is approximately 100 times as great as that of an electron; the alpha particles collide in their short course with a large number of molecules with a terrific impact and cause the dislodgement of negative electrons from the electronic systems through which they pass, thus ionizing and disrupting organic and inorganic molecules; and the destructive effect of alpha-rays is therefore much larger than that of beta- and gamma-rays, the ratio being 10,000 (alpha-rays) :100 (beta-rays) :1 (gamma-rays). The action of the alpha-rays is more powerful the more mesothorium there is contained in the paint in relation to the radium present, as the mesothorium in equilibrium with radiothorium emits five alpha-particles per unit of time, when radium gives off only one. Alpha-particles emitted by mesothorium and its degradation products have a higher velocity and therefore greater penetration power than those discharged by radium.

In evaluating the relative share, which the various types of rays given off by the radioactive substances deposited in the bones of the dial painters had upon the development of the osteogenic sarcomas, it must be remembered that these neoplastic manifestations are relatively late appearing reaction products, that is, they become manifest at a time when the mesothorium component has reached its half-time value (6.7 years), and when the actinic activity of the radium has not decreased noticeably. It is probable, therefore, that beta- and gamma-rays play an appreciable part in the production of the sarcomatous reactions. This conception is supported by the fact that radium predominated over mesothorium in the bones with sarcoma and was the only radioactive substance present in several cases.

The delayed appearance of the sarcomatous growths, which originate on the basis of a chronic radiation osteitis, does not favor the conception that these tumors are the result of a cellular mutation brought about by the action of the rays upon the chromosomic content of the periosteal cells. It seems to be more likely that the rays produce a substance of rather low carcinogenic potency in the exposed cells, which must act over a prolonged period until the carcinogenic cellular sensitization becomes permanent and fixed. The primary multiplicity of the malignant lesions frequently observed reflects the more or less generalized distribution of the causative material in the bones.

IX. DEMONSTRATION OF RADIOACTIVITY IN WORKERS

Radium or mesothorium deposited in solid form in the body produce emanation. In the case of radium the amount of radon generated is relatively small, as the greater part of it is held back within the solid, while some of

it escapes into the blood stream and is exhaled. Thoron, resulting from the disintegration of mesothorium enters the blood, appears in the exhaled air, and may be demonstrated there. Radioactive matter is contained, also, in the feces and urine of persons who ingest or have ingested radioactive substances.

For the determination of radioactivity of the body three methods are used: demonstration of gamma radiation, radon test, and thoron test (Ives; Knowles and Britten).

Demonstration of gamma radiation: The determination and estimation of gamma radiation emitted by radium and mesothorium fixed in the organs of living persons has been done by numerous investigators (Schlundt, Barker, and Flinn; Evans; and Braaten and Leitch), and can be done with one of two methods, electrometric method or the Geiger counter technique. The electrometric method is many times less sensitive than the procedure requiring the use of a Geiger counter (Flinn; and Martland), and is considered by some investigators as unsuitable for the reliable demonstration of the small amounts of gamma irradiation emitted from the body. The various technical modifications of the method employing the Geiger counter are not only much more sensitive (demonstrating less than 1 microgram per body) than the electrometric one, but are also much easier applied and less apt to give erroneous results (Flinn). The gamma-rays which are demonstrated by these procedures are emitted by radium C, the amount of which thereby determined permits the calculation of the quantity of radioactive material present in the body. It is essential for a correct and reliable determination of the radioactivity of the body of individuals who have been exposed shortly before the examination to radioactive substances, that they wash their entire body thoroughly, especially the haired parts, so as to remove any dust particles adherent to the skin or hairs, before the test is performed. It is pertinent moreover that they wear clothes which have had no previous contact with radioactive material.

Determination of emanation in the exhaled air: For the analysis of the exhaled air for emanation the individual exhales through a glass breath-sampling bulb. The breath must be held before exhalation into the bulb for a period of 30 seconds after a normal exhalation in order to permit the air remaining in the alveoli to approach radon equilibrium with the blood. An additional forced exhalation of this retained air is then passed into the sampling bulb. The radon content of this "alveolar air" is from two to three times higher than that of air exhaled without special effort (Evans and Aub). The radon containing air is passed from the bulb into an ionization chamber in which its alpha radiation is measured by means of an electroscope.

For the determination of the radioactivity of feces and urine, specimens of these materials are wet digested with nitric acid. The resulting liquid samples are boiled in a special reflex condenser for 20 minutes for the removal of radon. They are sealed afterwards for about four hours to permit the

accumulation of radon formed by the decay of the radium contained in them and then boiled again. The radon, which is boiled out, is conducted by a stream of nitrogen into an ionization chamber and its alpha radiation determined with the aid of an electroscope.

The total amount of radioactive material contained in a body is obtained by adding the quantity of radium required for the production of the radon shown in the exhaled air to the quantity of radium necessary for the generation of the gamma-rays emitted by the body and determined by the Geiger counter. Approximately 45 per cent of the body's radium is disclosed by the radon contained in the expired air, while 55 per cent is revealed by the gamma radiation leaving the body. This ratio remains constant with the passage of time. A measurement of the gamma radiation is therefore sufficient for a rapid estimation of the total radium burden in chronic cases (Evans and Aub). While 45 per cent of the decay products of radium are continuously removed with the exhaled air, only a very small fraction of the radium itself is eliminated from the body with the waste products (feces and urine). Flinn found that between three to ten years are required for the excretion of one microgram of radium, indicating that radioactivity of formerly exposed individuals is demonstrable for an extended period after cessation of contact with radioactive substances. According to the investigations of Aub and Evans, approximately 0.005 per cent of the radium deposited in the body is normally eliminated per day with the feces and urine [9 per cent of the total amount in the urine (range 7.5 to 10.5 per cent) and 91 per cent with the feces]. This ratio is constant, even when the normal excretion is increased manyfold by therapeutic measures.

X. PATHOLOGY

The macroscopical and microscopical changes observed in these dial painters with osteogenic sarcomas were described in detail and with great thoroughness by Martland. The post-mortem examinations performed on the girls with radium sarcoma revealed the presence of a radiation osteitis associated with a replacement of the yellow marrow in the long bones by a deep red marrow, such as seen in pernicious anemia, containing, however, greyish white areas of radiation osteitis. The radiation osteitis involved most often and markedly the vertebrae, which proved to be soft and woody on sawing in several cases. There were greyish white areas present consisting of a gelatinous or myxomatoid cellular fibroblastic tissue. The osteogenic neoplasms were partly well-circumscribed, partly ill-defined, and diffusely invading the adjacent soft tissue as well as bone and vessels. The greyish white, firm, sarcomatous tissue contained circumscribed pinkish to reddish areas. Spicules of bone tissue were found occasionally deep in the tumor tissue. The metastases were always free from osseous elements, and were found in the liver and lungs. They were encephaloid in appearance and consistency, reddish grey in color, and con-

tained yellow or hemorrhagic necrotic centers. The calvarium was hard and ivory-like, containing very little spongy bone. There were some oval, expansive areas on the inner table of the parietal bones present in some cases showing some cancellous bone with erosion.

The histological structure of the neoplastic tissue showed rather markedly anaplastic sarcomas, exhibiting with their numerous mitoses evidence of a rapid proliferative activity. There were certain variations in the structure of different parts of the same tumor as well as between different tumors. The medullary sarcomas were composed of an embryonic type of cell, and contained numerous giant cells of sometimes bizarre structure (Martland). Other tumors of fibrous appearance and firmer consistency consisted of more mature, fibroblastic-like cells, while in a third variety, osteoid tissue, bony spicules, and cartilagenous areas were found. One neoplasm displayed a myxosarcomatous structure (Flinn).

The bone marrow was composed predominantly of a megaloblastic type of cells mixed with numerous primitive, hematoblast-like cells. There were few mature erythrocytes and practically no neutrophilic myelocytes or more mature forms of the myeloid series, while an innumerable number of eosinophilic myelocytes together with megakaryocytes filled the marrow spaces. Lymphocytes were not found. The changes observed in the red parts of the bone marrow suggested that the immature cells failed to mature into granulated leucocytes, with the exception of the eosinophilic myelocytes and leucocytes, which did not appear in the circulating blood, presenting the picture of a neutrophilic agranulocytosis. Apart from the eosinophilic series only the erythrocytic cells approached maturition. Non-hemoglobinoferrous and hemoglobin-containing, nucleated erythrocytes were present in all stages from megaloblasts to normoblasts. There were anisocytosis, macrocytosis, polychromasia, and occasionally normoblasts and megaloblasts in the circulating blood, in addition to a general reduction of the erythrocytic elements. The cellular bone marrow was replaced in many places by a very cellular, fibroblastic tissue containing eosinophilic myelocytes, plasma cells, and lymphocytes with numerous mitotic figures. The tissue in such areas resembled closely that of a sarcoma. In more whitish parts the marrow consisted of an acellular, fibrous, sclerotic tissue, sometimes containing osteoid areas and representing apparently healed lesions of neoplastically inert replacement fibrosis. The cellular osteitic reaction furnished the basis for the sarcomatous responses.

The radioactive genesis of these cellular reaction products has been shown by the demonstration and determination of the causal substances in the bones and other organs. Various methods have been employed for this purpose. The method of self-photography by the radioactive organs is a quick, reliable, simple, and therefore most useful and indisputable approach in this respect, permitting a rough estimate of the amounts of radioactive material present and a determination of the exact location of the deposits (Martland).

For the performance of this test the bones are cleaned from any adherent tissues, then boiled with water to which a little sodium bicarbonate is added, rinsed with water and dried in a hot air oven. Standard photographic films in their original packet are then strapped over the bones with the film surface directed against the bone with adhesive. Metal paper clips or pieces of lead foil are interposed between the bone and the film surface of the packet. Through this procedure the alpha-rays are screened out and only the beta- and gamma-rays are permitted to act. The exposure time is long (between 15 and 25 days). When the film is developed radioactive bone produces a diffuse and focal fogging, indicating the distribution of the radioactive substances in the bone on the film, that shows the sharply outlined shadows of the interposed paper clips, which stand out as if they were photographed with roentgen-rays. The irregular distribution of the radioactive substances in a particular bone proves that calculations of the total content of radioactive substances present in a bone or in the entire skeleton are unreliable and misleading, when based upon the examination of a small portion of a single bone.

In a modification of this method, cleaned and dried bones or bone ash are placed directly on the surface of a superspeed or process Eastman film and kept there in absolute darkness under observation for 7 to 10 days when bones are tested, or for 30 days when ash is examined. The longer exposure of the ash is due to the fact that incineration deemanates the ashed material temporarily. The developed films show the characteristic irregular fogging or the definite alpha-ray pencilling, thus visualizing the deposits in their irregular distribution and concentration. An overexposure results in a diffuse fogging which obscures the distributory details.

Lacassagne, Lattés, and Lavedan have adapted this qualitative test to the examination of paraffin sections of bone tissue (autohistoradiography). The exposure time for such sections is from 15 to 20 days. The uneven distribution of the deposits of radioactive material in the bones and their peculiar concentration in the outer portions of the cortex can be shown by this method, which permits a comparison of the autohistoradiographs with corresponding, stained sections of the tissue prepared from the same block.

For quantitative measurements of the radioactivity of the various organs, the organic material has to be ashed. The alpha radiation emitted by the ash can be determined with an alpha-ray electroscope. For the determination of the gamma-rays the ash is mixed with barium chloride and hydrochloric acid and made into a paste. This paste is boiled first with hydrochloric acid, then with distilled water, and finally filtered, while still hot, through a hard filter paper. The precipitate on the paper is allowed to dry and is then incinerated together with the paper. The ash obtained and containing radiothorium is tubed and sealed and its radioactivity is determined with a gamma-ray electrometer. The filtrate is treated with sulfuric acid and allowed to stand until a precipitate is formed. The material is then boiled and filtered while hot so

as to hold the calcium sulfate in solution. The precipitate retained on the paper is dried and incinerated with the paper. The ash is tubed and its radioactivity is measured thirty days later with the aid of a gamma-electrometer. The second precipitate contains radium and mesothorium. The final filtrate should not be radioactive (Evans; Rajewski; and Martland).

The bones of radioactive individuals retain their radioactivity for many years after death. St. George, Gettler, and Muller were able to demonstrate radioactivity in the bones, liver, and lungs of a girl dial painter who had been interred for five years. Of the 48.4179 micrograms of radium found in the organs of this girl, 48.282 micrograms were present in the bones. Similar observations were reported by Rajewski. The quantity of radioactive substance demonstrated in lethal cases of radium poisoning ranged from 10 to 180 micrograms, in post-mortem material obtained from individuals who had died from three to eight years after discontinuation of the hazardous work (Martland). While the relative content in the different organs of radioactive material may vary a great deal from case to case, the bone marrow, the bones, and the spinal cord contain the largest amounts, much less being present in the brain, lungs, liver, and spleen, and still smaller quantities are found in the heart, stomach, and intestine. Evans placed the different organs, when arranged according to their relative content of radioactive material, in the following order, giving the vertebrae the arbitrary value of 100: vertebrae, 100; jaw, 51; femur, 48; tibia, 30; skull, 18; brain, 0.4; liver, 0.5; spleen, 0.9; and lungs 2.2.

The amount of radium present in persons showing the symptoms of radium poisoning was estimated to vary between 2 to 20 micrograms using the electrometric method. The amount of radium which causes an irreparable tissue injury was placed below 1×10^{-9} gm. radium per gram tissue.

XI. EXPERIMENTAL OSTEOGENIC SARCOMAS OF RADIOACTIVE GENESIS

The repeated experimental production of osteogenic sarcomas, following the introduction of radioactive material (mesothorium and radium) into subperiosteal and medullary tissue of bones, has confirmed the clinical observations concerning the cancerigenic effect exerted by these substances upon the osseous tissues. Alpha-, beta-, and gamma-rays share these properties equally and the neoplasms produced are in general the results of the combined irradiation (Uehlinger and Schürch). These investigators placed, in their first experimental approach, a radium needle of 1 mgm. underneath the periost of the mandible of a rabbit leaving it in place for 15 days on one side and then shifting it for 20 days to the other side, delivering 360 and 480 mgmhrs., respectively, of mainly beta-irradiation. While the dose administered is comparatively small, when compared with the amounts given by other investigators in the experimental production of sarcomas in other organs, there developed a swelling of the mandible on the side exposed for 20 days after

an interval of 18 months. The rapidly, infiltratively, and osteolytically growing tumor proved to be a spindle-cell sarcoma, originating from the periosteal tissue and characterized by a marked irregularity in the size and shape of the component cells. Areas of cartilaginous, osteoid, and osseous tissue were found within the neoplastic tissue.

The same investigators, using in a subsequent experiment twenty-two rabbits, placed into a small cavity, which they had chiselled into the trochanter of the femur, a plug of radioactive vaseline which contained in fourteen cases 2 to 5 micrograms of radium, and in eight rabbits similar amounts of mesothorium. The first osteogenic sarcoma in the exposed bones was observed 19 months later. A total of 5 sarcomas was obtained, that is, 31 per cent of the treated animals (22) developed tumors. Three of the sarcomas were of the osteoplastic type, while the two others were spindle or polymorphous cell sarcomas, the latter forming earlier widespread metastases than the former. There were no secondary neoplastic deposits in other bones, while ossifying and non-ossifying metastases were found in the lungs, spleen, liver, kidney, stomach, thyroid, and in numerous lymph nodes. The experimental tumors conformed therefore in metastatic respects to the osteogenic sarcomas seen in man. The metastases did not contain any radioactive material.

In a third communication, Uehlinger and Schürch reportedly obtained sarcomas in 50 per cent of the animals surviving the exposure to radioactive material a sufficiently long time. There were nine sarcomas present, four were fibrosarcomas, four were differentiated osteogenic sarcomas, while one consisted of large oval cells of rather uniform size, basophilic cytoplasm, and large oval nuclei with dust-like, chromatic nucleoli. This neoplasm had no stroma, but many necroses present in the greyish-white nodes were found in the marrow of several bones, the lung, kidneys, liver, spleen, and ovaries. The tumor was considered a reticulum-cell sarcoma of the bone marrow (Ewing's tumor).

In a subsequent report of Uehlinger and Schürch published in 1938, these investigators had obtained metastasizing osteogenic sarcomas in fourteen out of twenty-one rabbits with implantations of radioactive material into the femur. The variations in the dose (0.0001 to 0.0005 mgm. of mesothorium) used in the different animals did not influence the incidence and latency period of tumor formation. Mesothorium and radium displayed the same cancerigenic effects. The lethal period varied from twenty-one to twenty-nine months for the different animals.

Similar results were obtained by Sabin, Doan, and Forkner, who injected five rabbits intravenously with 5.1 micrograms of radium chloride weekly and four rabbits with 7.7 micrograms of mesothorium once a month. Of seven rabbits surviving for 11 to 19 months, two exhibited osteogenic sarcomas. One of the cancerous animals, which had received 14 injections, showed radioactive, brittle bones containing a gelatinous, aplastic marrow in the long bones, while

others had a hyperplastic marrow. There was an increased vascularity between the bone and the marrow. The sarcoma involving the humerus contained numerous multinucleated giant cells and developed after 15 months from the start of the experiment. The second sarcoma appeared in the lower end of the femur of a rabbit, which had received 6 injections of mesothorium within 11 months, and was an osteoblastic sarcoma with many giant cells.

Jentzer reported in 1936 a sarcoma from the bones of the skull of a rabbit after the application of radium. Ross, who implanted into the thoracic wall of nine young rabbits radium needles, containing 0.1 mgm. of radium screened by 0.5 mm. of platinum for obtaining an almost pure gamma radiation with little beta-radiation, produced malignant neoplasms in six animals after two years of exposure. One of these reactions was an osteogenic sarcoma of the ribs, two were spindle-cell sarcomas, one was a myxosarcoma, and two were squamous-cell carcinomas.

Bauer mentioned a spindle-cell sarcoma of the femur of a guinea pig two years after the implantation of mesothorium. Daels and Biltris introduced by trepanation into the cavity of the skull of guinea pigs a mixture of radium with paraffin, diatomaceous earth, and arsenious acid, and observed after 15 months and 30 months, respectively, in two animals the development of a tumor, one being a periosteal fibrosarcoma, and the second, a meningeal osteogenic sarcoma. Hellner produced an osteogenic sarcoma of the region of the knee in a rabbit which had received 2,480 mgmhrs. of radium over the region of the knee joint. The neoplasm was an osteoplastic, spindle-cell sarcoma with areas containing polymorphous and giant cells, and produced pulmonary metastases.

The experimentally produced osteogenic sarcomas of radioactive origin resemble histologically and biologically the corresponding tumors observed in man under occupational conditions. The latency period of the experimental sarcomas is somewhat shorter (11 to 36 months) than that of the human radium sarcomas (upwards to 60 months). The difference observed does not show a proportional relation to the difference in the normal life spans of man and rabbits.

XII. PROGNOSIS

The prognosis of radium poisoning caused by the oral ingestion of radioactive substances depends upon the amounts retained in the organs, and upon the character of the radioactive material introduced. The prognosis is not quite as serious when mesothorium is present as when radium is stored. The half-time of mesothorium is 6.7 years, that is, the radioactivity of this substance is spontaneously cut in half after the elapse of this period, while there occurs no appreciable decrease in the radioactivity of radium within the lifetime of human beings, as the half-time of radium is 1,750 years. If a radium poisoned individual survives the more acute hazards, resulting from the development of an anemia or septicemia, his ultimate prognosis is determined by the po-

tential development of an osteogenic sarcoma, and depends upon the fact, whether or not it is possible to remove by therapeutic procedures the radioactive matter from the bones before it is able to elicit a neoplastic response. The prognosis, once the neoplastic process has become established, is absolutely infaust, especially so, as the sarcomatosis is multifocal and cannot be influenced effectively by the therapeutic measures available.

XIII. THERAPY

The therapeutic procedures indicated in chronic radium poisoning must be directed toward the removal of the radioactive material deposited in the body. Since the radium stored in the bones is present in a combination similar to that found with lead, the therapeutic management of radium poisoning has been based upon the treatment devised for the mobilization of lead from the bones, and its elimination with the urine and feces. Flinn (1927) first adopted such procedures, when he treated one of the dial painters for four days with ammonium chloride and reduced the radium content of the body from an estimated 100 micrograms to 86 micrograms.

Elaborating on this type of therapy Flinn and Seidlin administered subsequently to three cases with radium poisoning, parathormone by injection. In one case there was a loss of radioactivity of 45.6 per cent within 7 weeks, in a second case the reduction of radioactivity amounted to 57.7 per cent obtained during a corresponding period, while in the third case a decrease of 50.5 per cent was noted. Parathormone was given to these patients every other day in doses starting with 10 units and gradually rising to 50 units intramuscularly. Blood calcium determinations were performed frequently before the injection of parathormone. With a combined treatment of ammonium chloride and parathormone, Flinn noted the excretion of 1 microgram every 60 days (2,200 micromicrograms with the urine and 16,000 micromicrograms with the stool).

On account of the various disadvantages which are connected with the use of this method, Flinn turned to viosterol, beginning with a few drops orally and increasing gradually until a dose of a teaspoonful three times daily was reached. Eight patients, having a radium content ranging between 10 to 90 micrograms, subjected to this management showed a marked reduction of the radioactivity or a complete disappearance of this phenomenon in the milder cases within four years (electroscopic test), and simultaneously the radioactivity of the exhaled air decreased remarkably (in one case to one/thirty-fifth of the original value). The difficulty connected with this massive type of medication lies in the fact that there is an already damaged bone present, which undergoes under the influence of an intensive treatment of the above-mentioned type further decalcification. The administration of 20 to 30 drops of viosterol three times daily may obviate such undesirable effects, while extending the period of elimination of the radioactive substances.

Craver and Schlundt, who gave smaller doses of parathormone and viosterol, than those used by Flinn, to four patients, observed only a slight increase of the excretion of the radioactive material following the injection of parathormone, while no such effect was noted after the administration of viosterol. Evans and Aub placed four cases of radium poisoning, one of them a dial painter, on a therapy of parathormone, viosterol, and low calcium diet. Whereas the blood calcium level was kept normal through this procedure, the excretion of radium was increased fourfold over the original level. Similar results were obtained in the dial painter by the administration of ammonium chloride and thyroid extract alone. Flinn found that the administration of liver and iron preparations and blood transfusions does not produce any permanent improvement in the hematic status of such patients. A calcium therapy is indicated, except when elimination of the radioactive material is to be stimulated.

XIV. PREVENTIVE AND SANITARY MEASURES

The technical preventive and precautionary measures recommended for the prevention or reduction of an occupational contact with radioactive material must be observed in the laboratories in which radioactive substances are manufactured and purified, and in the industrial establishments in which these preparations are used for various industrial, commercial, and military purposes.

Morris; and Schlundt, McGavock and Brown described the technical procedures followed and the precautions taken in laboratories in which radioactive substances are purified. During the process of refining by fractional crystallization the exposure to radiation is decreased by keeping the radioactive salts in solution or in contact with liquids at all times, so that the alpha-rays are entirely stopped and the beta-rays are almost completely absorbed by the dishes, solvent, and air. All open treatments and heating processes are carried out under the hood having a forced draft, so as to minimize the possibility of inhaling or ingesting active compounds. Ventilating fans are kept running constantly during workings hours and the windows are kept open as much as possible. During the final stage of the crystallization at which highly active preparations are handled, the evaporating dishes are placed in thick lead shields for reducing the danger from gamma-radiation. Whenever the dehydrated salts have to be handled, carrying with it the possibility of inhaling radioactive dust, the work is carried out in a hood with a large piece of plate glass interposed between the worker and the active material. The tubing of active compounds is done in a glass case with a door just large enough to admit the hands of the operator. The crucible containing the active compounds and the tube are held during the manipulations with special holders.

While these arrangements decrease the danger from alpha- and beta-rays to a minimum, there remains an appreciable hazard from an exposure to

gamma-rays, so that workers handling high-grade materials frequently develop burns of varying intensity on the thumb and index finger. The radioactivity of the air and of the dust in the plant is determined, so as to test the efficacy of the precautionary measures taken and to keep the radioactive content of the air at a minimum. Photographic films are carried by the workers on their body to show the effects of an exposure sustained during the crystallizing processes. The workers are required to wear dust masks or a towel over their mouth and nose whenever dry material is handled. They are requested to wash their hands at frequent intervals and to clean their nails with a brush before leaving the plant. Blood examinations are performed at six month intervals. The radioactivity of the body of the workers is ascertained, also. It was found that this factor varied greatly in different individuals, and that the emission of alpha-rays dropped after vacations and was increased in the exhaled air during periods of colds, decreasing considerably after such attacks.

The study of the situation existing in American luminous dial plants by Stewart from the Department of Labor, and by Schwartz, Knowles, Britten and Thompson from the Public Health Service led to the following suggestions for minimizing the hazard in these studios:

Apart from stressing the importance of extreme cleanliness in the workrooms and of the personnel in conjunction with adequate general and local ventilation, Schwartz, Knowles, Britten and Thompson made these proposals: 1. Rigid and continuous inspection of all processes involving the use of radium supervised by a qualified officer, responsible directly to the plant management; 2. Painting by hand should be done by a method which will eliminate the contamination of the mouth and fingers with radium (use of a glass stylus or pen in place of a brush); 3. Styluses or pens should be wiped on cloths or other suitable material kept moist with a solvent (rubber sponge kept moist with a solvent held in a small container); 4. Racks should be provided so that pens, styluses, or stirring rods may be held securely, preventing contamination of the work places with paint from this source; 5. Paint containers should not be over 0.5 inch deep and should be placed in a holder so that retaining them in the hand is unnecessary; 6. Dry paint should be mixed with liquid ingredients in a hood with openings for the hands only, and provided with suitable exhaust ventilation to prevent the escape of dust or emanation into the workroom atmosphere; not more than a day's supply of paint should be mixed at one time and it should be kept covered in a container lined with lead at least one inch thick; 7. In order to avoid any accumulation of radioactive materials in the workroom, mixed paint and materials should be given out in quantities to last for a short period (1 hour or less), all material and empty containers to be returned at the end of each period; 8. All utensils should be cleaned moist. Discarded material should be removed promptly from the workroom; 9. Moist methods only should be used

for removing paint from surfaces and in recovering radioactive material from old or rejected stock; cloths used for this purpose should be replaced by fresh ones twice daily; and material collected should be segregated under lead protection in closed containers; 10. Radium material should be stored in containers shielded by lead and kept as distant as possible from the workers; the lead should be one inch thick; 11. The room in which the painting processes are carried out should be separate from those used for other purposes; 12. Floor and work places should be constructed so that they may be thoroughly and readily cleaned by a moist method; they should be cleaned daily after work hours; pipes and window sills, which collect dust should be cleaned weekly with moist method; flooring should be of such a type and condition that it is easily cleaned and has no cracks and crevices for the accumulation of dust; and work tables should be of some polished and easily cleaned material (enamel); 13. Ample space should be provided for each worker; 14. Good illumination (10-foot candles on working plane) should be furnished; 15. Drinking water should be supplied from a bubbling fountain (no drinking cups); 16. There should be convenient washing facilities (one for each five workers) with a cold-hot mixing faucet, with paper towels and brushes; 17. Only neat and careful persons should be employed; 18. Clean smocks laundered at regular intervals should be provided; 19. Hands should be scrupulously clean at all times, a foreman should see to that; 20. Eating utensils and eating during working hours in workrooms should be prohibited; 21. Workers should clean hands with a brush before eating and after work under supervision that this regulation is properly carried out; 22. Adequate general ventilation (15 to 20 times per hour) and additional local exhaust ventilation, where radium concentration is high, should be installed; 23. Painting by hand should be done beneath a sheet of plate glass having a convex-lens at least three inches in diameter cemented to its lower surface; the glass should be large enough to cover all the radio-active material; the lens should be of such a focus that the face of the worker is not less than 14 inches from the work (local exhaust ventilation should be applied beneath the glass); 24. Anyone who weighs, mixes, or distributes radioactive substances should be protected by suitable screens (lead) and from dust by ventilated hoods; 25. Inspectors of radium painted stock should conduct their work at open front cabinets provided with an exhaust ventilation of sufficient quantity to secure an air movement of 100 to 200 linear feet per minute at the face of the cabinet and in a direction toward its back; 26. Because of the high dust concentration, dusting and transfer press work as observed should be abandoned or adequately safeguarded; 27. To test the effective enforcement of precautionary measures periodic examinations at least annually, including electroscopic tests (gamma-ray and radon), blood examinations, x-ray pictures of the maxilla and mandible, and test of the radioactivity of the workroom air are advised; the results of these examinations should be communicated to

the employees; and 28. A statement of the precautions to be taken by the workers for the prevention of radium poisoning should be posted in the workrooms; all applicants for work should be advised of the hazard and instructed in the observance of necessary precautions.

A similar elaborate set of precautionary and preventive measures was proposed by Stewart, who suggested several procedures through which the manufacture of luminous dials might be mechanized to a higher degree and the existing health hazard be reduced (use of revolving brushes for the removal of excess paint; removal of excess powder by an exhaust ventilation to be recovered later, thereby preventing any radioactive dust to escape into the workrooms; use of a mechanical method of application of the radioactive material by the use of transfer presses, employing a steel-die stamping press with a resilient transfer pad; and rotation of workers through the different departments to reduce time of marked exposure.

In the Federal establishment where dial painting is performed the following rules for the safeguard of the health of the employed workers were issued by the Bureau of Aeronautics of the United States Navy Department (Stewart):

1. All personnel employed in repainting luminous symbols of instrument dials, or other work requiring the use of radium luminous paint, will be instructed in and required to observe the precautions necessary for reducing the chances of harmful effects from this material.

2. The precautions, as promulgated by the Bureau of Medicine and Surgery, are quoted below:

"Radioactive materials are considered poisonous because if an individual is exposed to high concentrations for long periods of time, there will result disease processes which may become fatal."

"The effect upon the body is principally lowering the resistance to infection by a change of the relative percentage of white corpuscles in the blood and bone marrow. Persons with poorly preserved teeth and sufferers of chronic constipation are particularly subject to the harmful effects of radioactive substances."

"Exposure is principally through the mouth by swallowing and the inhalation of gases highly laden with the particles. In the concentrations used in the preparation of luminous dials, where only small portions are placed close to the handlers there is little danger of deleterious effect from direct exposure."

"The following instructions are suggested as reducing the chances of harmful effects:

a. Only persons free from diseased teeth and free from chronic constipation should engage in the handling of the material.

b. Daily handling should not extend over a period of more than three months, when worker should be assigned to other work for an equally long period.

c. Handlers should scrupulously avoid: 1. pointing brushes with lips; 2. touching the face or food with soiled hands; 3. touching radioactive substances except by instruments.

d. Handling should be conducted in well-ventilated and well-lighted rooms.

e. Handlers should be frequently examined, particularly for; 1. Leukopenia (particularly actual reduction in the number of neutrophiles); 2. Lowered blood pressure; 3. Anemia with high color index; 4. General physical examination and careful dental examination."

Stewart stated that even in the best conducted plants his recommendations have not been introduced *in toto*.

XV. MEDICO-LEGAL ASPECTS

In regard to the medico-legal aspects of these occupational neoplasms, Martland was prompted to make the following remarks:

At the time the cases of radium poisoning were discovered in New Jersey this state had no compensation laws covering this occupational hazard. It was argued in the ensuing court procedures by the defendant company which had been sued by the victims that it had been unaware of the hazard involved and that no information on such a danger had existed up to that time, that it was not guilty of negligence. A financial settlement was reached ultimately by a compromise rather than by application of a law. Martland noted furthermore that the radium cases should be looked upon as an unfortunate but valuable experiment in which, through ignorance and lack of proper governmental supervision, human beings have been allowed to swallow, over long periods of time, radioactive substances. He expressed the hope that knowledge of the causation of this disease would be followed naturally by an abolition of the risk, causing this occupational neoplasm to disappear, while it would remain important for the light it had shed upon the occurrence of anemias, on the etiology of malignancy, and the close relationship of certain blood dyscrasias. Evans expressed himself in a similar vein, when he remarked, that radium poisoning was in most cases the result of uninformed carelessness in an occupation, in which protective measures have now been taken.

While it appears somewhat uncertain whether these optimistic hopes will be fulfilled, it is certain that no party will be able to claim in the future again ignorance of the dangers connected with the handling of radioactive substances, for the purpose of avoiding the moral and legal obligations which might arise from an improper handling of these compounds. The occurrence of the blood diseases and osteogenic disorders has caused the introduction of special compensation legislation in various states (including New Jersey) applying to these occupational hazards. Objectionable laws exist in this respect in some states, where the delay period is by far too short to provide any adequate protection for the workers. In France, for instance, bone necrosis by radio-

active substances must become manifest within one year following cessation of work with these substances (Laborde). It is obvious that such restrictions are apt to defeat the purpose of the law and the moral background of the legislation in many cases of radium poisoning, especially where osteogenic neoplasms are concerned.

c. Roentgen-Rays

Occupational exposure to roentgen-rays has not given rise to the development of osteogenic sarcomas, according to the information available. It is not likely that such lesions will result under the conditions of exposure prevailing under ordinary circumstances, as the type and amount of rays entering the body are not suitable and sufficient to elicit neoplastic responses in the deep-seated osseous tissues.

There exists satisfactory clinical and experimental evidence attesting that roentgen-rays may elicit such reactions under proper conditions of exposure. There are first the sclerotic and porotic responses of the osseous tissue to roentgen irradiation, known as radiation osteitis and representing, as seen in the radium sarcomas, a preparatory stage for malignant sequelae. The occurrence of an appreciable number of osteogenic sarcomas, originating from the irradiated tissue of tuberculous joints subjected for therapeutic reasons to an intense treatment with roentgen-rays, provides additional evidence of the cancerigenic effects which this form of radiating energy may exert upon the osseous tissue (Beck; Brandt; Brandes; Baumann; Martin; Pförringer; Deuticke; Küttner; Heidrich; Hellner; Becker; Bancklund; and Hanke and Neuhaus). Osteoid and chondroid elements were found in the spindle cellular or polymorphous cellular sarcomas developing on this basis and exhibiting a marked degree of malignancy. The latency period in a series of 17 cases was from five to eleven years and the development of the neoplastic process ensued at a time, when the tuberculous changes had healed completely. In view of this and considering that the sarcomas develop from the tissue of the epiphyseal line, as they are usually composed of chondro-fibro-osteoid tissue, and not from somewhere within the large area of injured tissue, it is probable that the tuberculous process plays a nonspecific, minor, contributory and preparatory rôle in the genesis of these neoplasms. These therapeutic roentgen-sarcomas of the bone affect most often the knee joint of young individuals (Becker). For these reasons, Hellner cautioned against the subjection of the epiphyseal tissue to a prolonged and intense roentgen-irradiation.

Similar neoplastic responses of the bony tissue have been elicited by roentgen-irradiation in animals. Lüdin, who exposed the tibia of a rabbit to a total of 8,000 r delivered in 40 treatments given in five day intervals, obtained after six and a half months an osteolytic chondrosarcoma. Lacassagne and Vinzent observed the development of an osteogenic sarcoma in the femur of a rabbit six and a half months after the irradiation of a bacterial abscess produced adjacent to this bone with roentgen-rays (1,000 r). A periosteal fibrosarcoma

of the femur of a rabbit was produced by Lacassagne, which developed 36 months after the treatment of an abscess near the bone with a total of 1,980 r delivered in three doses (915 r; 444 r; and 610 r).

The clinical and experimental observations recorded indicate that roentgen-rays may incite sarcomatous responses of the osseous tissue under proper conditions of exposure, particularly when a chronic inflammatory process is acted upon.

d. Physical Trauma

Single physical trauma of accidental nature as well as repeated injury of occupational origin display a definite causal relationship to the development of certain pseudoneoplastic and neoplastic lesions of the cartilagenous and osseous tissues.

Pseudoneoplastic Reactions: Traumatic osteochondromatosis (osteochondritis dissecans). Solitary accidental trauma and particularly repeated occupational injury, such as exerted by the vigorous vibrations set up in the joints of the arm during the use of tools driven by compressed air (drills and hammers), have been shown to be responsible for the causation of an intraarticular disorder known as osteochrondromatosis of joints or osteochondritis dissecans. This condition, which is characterized by the appearance of multiple, small bodies of cartilagenous or osteo-cartilagenous tissue within the articular cavities, resulting from the traumatic destruction and splitting off of parts of the cartilagenous articular lining, is seen most frequently in workers using pneumatically driven tools (miners, road workers, ship builders, and construction workers) (Muller and Gernez; and Bürkle-de la Camp).

Occupational or accidental trauma was incriminated in 44 per cent of the 112 cases analyzed by Muller and Gernez, but a possible traumatic origin was acknowledged in only 19 cases. Bürkle-de la Camp emphasized that a constitutional factor plays a significant rôle in the genesis of this disease, as it is found especially often in manual laborers of robust, muscular build and of the male sex (80 per cent). The age range in which this condition is found is from 16 to 76 years, while the peak of frequency occurs from 20 to 40 years of age. The development is slow and the symptoms appear late after the traumatic episode, usually after the demonstration of the intraarticular bodies [3 to 20 years of latency in 57 cases (Muller and Gernez)]. The chondromatous condition most frequently affects the shoulder joint (50 cases), less frequently the knee (39 cases), and other articular cavities (elbow). The symptoms observed are pain in the joint, impaired motion, sensation of a foreign body in the joint, swelling of the articular region by a reactive hydrarthros, and, in cases in which a traumatic contusion of the articular region resulted, in a new formation of extraarticular osseous tissue and deformation of the joint. Extraarticular bone formation may cause, in addition to deformation and limitation of motion, symptoms resulting from pressure upon adjacent

blood vessels and nerves. The articular surfaces of the affected bones exhibit cartilagenous erosion and eburnation of the bony tissue. A malignant transformation of these intraarticular cartilagenous and osteo-cartilagenous bodies has not been recorded.

In the evaluation of such articular disorders, especially for medico-legal reasons, consideration must be given to the fact that there occur in the joints of the wrist and foot anatomical variations in the number and configuration of the composing bones (supernumerary bones: divided scaphoid and semilunar bones, secondary os calcis, and os peroneum), which may be mistaken for traumatic osseo-cartilagenous fragments (Watkins).

Traumatic Exostoses and Ecchondroses. Cartilagenous and osseous hyperplasias of a tumor-like character (exostoses and ecchondroses) are recognized sequelae of traumatic hemorrhages into the periosteal tissue. They represent inflammatory metaplasias of excessive reactive proliferations of the periosteal tissue, which become secondarily calcified and ossified (ossifying periostitis) (Sauerbruch; Ewing; Phélip and Dillenseger; Graef; Delbet and Brault; Brunschwig; Ophüls; Fischer-Wasels; and Würz). A chondrofication and ossification of the young, proliferating, periosteal, connective tissue is favored by the presence of necroses and congestion. The center of the osteomatoid formation is usually an adult tissue, while the peripheral parts are of immature character. The bone formed is compact, hard, and lamellated. The individual lamellae are separated from each other by connective tissue. Spongy bone and myeloid tissue with giant cells is rarely formed. These traumatic osseous and cartilagenous reactions do not display any continuous growth, but become stationary after a varying length of time. Exostoses and ecchondroses of traumatic origin cannot be distinguished always and definitely from similar formations of bacterial inflammatory nature or hereditary genesis (congenital multiple ecchondromas) (Pels-Leusden; Ehrenfried; Honeij; Cox; Gorsline; Maynord and Scott; and Dwyer). The histological differential diagnosis between traumatic osteo-chondromatous outgrowths and malignant osteochondromatous lesions is sometimes difficult.

Special mention may be made of the traumatic exostoses involving the internal and occasionally the external condylus of the distal end of the femur (Pellegrini-Stieda disease) (Gautier; Guillaume-Louis; Bressot; and Minue and Marchand-Alphant).

Osteogenic sarcomas may develop after the elapse of a varying length of time, following the formation of a traumatic ossifying periostitis. (Geschickter; and Robert-Didier).

Traumatic Excess Callus. The formation of an excessive amount of callus may result as a sequela of an imperfect immobilization of a bony fracture, and appears occasionally without such a complicating factor being present. The callus tissue formed consists of an atypical osseous and cartilagenous tissue of sarcomatoid appearance, generated by the very active proliferation of the

endosteal and periosteal tissue in the region of the fracture. An exuberant callus represents a recognized source of benign as well as malignant neoplasms of the osseous and bony tissue.

Localized Osteitis Fibrosa and Giant Cellular Sarcoid Granuloma. An injury to the cancellous bone, often not sufficient to cause a breach in the continuity of the surface of the bone but resulting in a hemorrhage into the cancellous tissue, may lead to dystrophic reactions of repair and regeneration, which give rise to the formation of a localized osteitis fibrosa cystica or a giant cellular granuloma (giant cell sarcoma; brown tumor) in the marrow cavity of the affected bone (Sauerbruch; Brailsford; and Glauner).

These pathological reactions ensue when the injured bone is deprived of its normal trophic influences, causing a localized liberation of the calcium and an absorption of the trabeculae in conjunction with the formation of a mucoid fibrous bone marrow nearby, extravasations, congested and proliferated capillaries, and callous formation. Depending to some extent upon the type of trauma and the site of the injured area, these changes may lead, by an increased disintegration of the osseous tissue, to the formation of cysts within the bone or may be followed by so-called "brown tumors," which consist of a vascular, spindle cellular tissue containing many foreign body giant cells and old blood pigment (hemosiderin). While osteitis fibrosa is found mainly in the metaphyses and diaphyses of the humerus, femur, and tibia, giant cell granulomas are chiefly situated in the lower epiphyses of the radius and femur (Freund and Meffert; Pommer; and Lang).

Localized fibrous osteitis is distinctly a traumatic disease of the young, being most prevalent during the first and the early part of the second decade of life, while the giant cells granulomas are found mainly during the second and third decade. Lang stated that hemorrhagic traumatic cysts of the bones are found especially frequently in the growth regions of these organs of young individuals (Ewing). Inasmuch as the cellular changes observed in osteitis fibrosa resemble those seen in the bone marrow of many cases of osteogenic sarcoma of adolescent individuals, it is generally assumed that osteitis fibrosa is a precursor of osteogenic sarcomas occurring during the early periods of life (Ewing).

Neoplastic Reactions: Benign Traumatic Tumors. Chondromas and osteomas are rarely etiologically related to traumatic episodes. This is particularly true in regard to the hereditary multiple types of these neoplasms. It has been maintained, on the other hand, that a local trauma may activate a misplaced focus of cartilagenous tissue, situated in the epiphyseal region, into a neoplastic growth (Ophüls; Morton; and Duvior and Pollet) of solitary type. Traumatic chondromas of the knee and finger were reported by Müller; Loenhard; and Kaufmann. Brunschwig pointed out, however, that osteochondromas and osteomas of the hands and feet are rare, in spite of the fact that trauma to these parts of the body is frequent. Special mention may be

made of the callus enchondromas developing from the chondroblastic, regenerative proliferations of the endosteal tissue, as they exhibit a definite tendency to a malignant transformation, particularly when they are located in the femur and humerus (Simon; and Geschickter).

Malignant Traumatic Tumors. "The etiological significance of a single isolated trauma in connection with the causation of sarcoma has been more nearly settled as to osteogenic sarcoma than concerning a sarcoma of any other organ" (Scudder). While this statement has not found general acceptance (Hellner), there are indeed few investigators who deny entirely that trauma may exert directly or indirectly a causal influence upon the development of osteogenic sarcomas.

The most convincing cases of this type are doubtlessly the so-called "callus sarcomas," that is, malignant growths originating from atypical callus tissue formed as the result of traumatic fractures (Sauerbruch; Möller; Pick; Güterbock; Tausch; Finotti; Fischer-Wasels; König and Seifert; Simon; Borst; Jordan; and Giger). The length of the latency period of these neoplasms varies, according to Jordan, with the malignancy of the tumor formed, and may be as short as a few weeks. The sarcomas originating from callus are histologically osteoplastic, fibroplastic, or chondroplastic sarcomas. A keloid-like character is seen occasionally (Haslhofer and Lang).

Similarly convincing, as to the etiological relationship between trauma and osteogenic sarcoma, are the malignant neoplasms arising on the basis of a chronic traumatic osteomyelitis (Harbitz; and Simon). Scheid collected 16 cases of osteomyelitic sarcoma of the bone from the literature. None of these tumors showed a latency period of less than ten years. The malignant neoplasm appeared usually after the osteomyelitic process had existed for 30 to 40 years.

A third group of traumatic osteogenic sarcomas is represented by chondromyxosarcomas, arising from exostoses or benign central chondromas in adults having a history of a preceding trauma dating back from 2 to 25 years (Geschickter).

A fourth group of allegedly traumatic, osteogenic sarcomas are malignant tumors derived from originally benign, giant cell sarcoids (brown tumors) of the bone, that is, from the dystrophic repair tissue of intraosseous hemorrhages (Jentzer). While the question of a secondary, malignant, metaplastic transformation of brown tumors has been widely discussed from the viewpoint of a possible existence of a primary malignant variant of giant cell tumors of the bone (pro: Ewing; and Stone; con: Geschickter and Copeland), a great number of investigators concede that osteogenic sarcomas develop occasionally secondarily from these granulomatous foci (Korchow; Ewing; Kolodny; Troell; Simmons; Matz; Pierce; Kokita; Bower, Clark and Davis; Coley; Drerup; Geschickter and Copeland; and Glauner). Coley estimated the incidence of a malignant transformation of giant cell granulomas of the bone to

be in the neighborhood of 15 per cent, while Troell placed this figure at 8 per cent. Corresponding with the age incidence of the primary, benign, granulomatous, giant cellular reactions and the related osteitis fibrosa cystica, these osteogenic sarcomas are found most frequently in individuals between the age of 15 to 30 years (Coley). Ewing called attention to the frequent presence of osteitic fibrosing changes in the bone marrow adjacent to the sarcomatous intraosseous growths, thus indicating their derivation. The histological evidence of a malignant transformation of a brown tumor consists of the demonstration of a marked cellular polymorphism, of a clumping of nuclei, of the presence of atypical mitoses, and infiltrative and destructive growth (Geschickter and Copeland; and King). The metastatic deposits of osteogenic sarcomas originating in giant cellular granulomas do not contain, as a rule, any giant cells.

Additional evidence in support of the potentially malignant character of brown tumors may be found in the fact that sarcomatous complications, sometimes of multifocal nature, have been observed in connection with Paget's disease of the bone, in which a spongy, cystic, granulomatous tissue is found in the affected bones (Pick; Speiser; and Gerstel and Janker). Speiser estimated, from a statistical analysis of a series of 150 cases of Paget's disease, that the chances for an osteogenic sarcoma were 30 times greater in the individual with Paget's disease than in a normal person. Codman stated that 8 per cent of all cases of Paget's disease, which mainly involves individuals over 40 years old, exhibit a sarcomatous condition ultimately.

Traumatic periosteal sarcoma arises presumably from the outer layer of the periost, following a contusion and hemorrhage into these tissues. Winkler pointed out that in allegedly traumatic bone sarcomas, there is usually not a preceding extensive destruction of tissue present, but there seemed to have existed a post-traumatic, prolonged state of hyperemia. It was stated by Ewing that true periosteal sarcomas are composed of small spindle-shaped cells and seldom or never contain any trace of bone or callus, while traumatic periosteal sarcomas consist of large polyhedral cells and large spindle-shaped cells, occasionally mixed with mononuclear giant cells, and form, as a rule, a poorly developed, cartilagenous, bony tissue. A bony scar or a splinter has been found in some instances within the sarcomatous tissue developing after a trauma (Sebestyen). This investigator estimated that approximately 4 per cent of all osteogenic sarcomas were of traumatic origin. Troell felt that the possibility of a traumatic factor entered in one out of every 6 to 7 osteogenic sarcomas. Kolodny and Putti were impressed by the frequency of a trauma in the history of bone sarcomas.

In spite of the evidence cited in support of a traumatic origin of the various types of osteogenic sarcomas, it is quite apparent that such a sequela of a trauma to the bone is a rare exception. The absence of any appreciable increase in the frequency of traumatic osteogenic sarcomas after the World War emphasizes

this fact (Troell). It is probable that important additional endogenous or exogenous factors must be active and present to bring about the neoplastic response to a traumatic local, nonspecific disturbance in the bony tissues.

Ewing called attention to the contributory role which nutritional, circulatory, and secondary developmental disturbances of the bones, caused by avitaminotic conditions (scurvy and rickets), may play in this respect. Fenster also emphasized the importance of congenital malformations of the bony tissues as sources of subsequent malignant developments. The significance of disturbances of a congenital nature is illustrated by a communication of Werner, who observed in several members of a family exhibiting a tendency to multiple fractures, the ultimate development of sarcomas, apparently superimposed upon the chronic traumatic changes in the bones. Roberts and Roberts noted the concurrent development of osteogenic sarcomas in a brother and two sisters, following a traumatic episode in two of the three affected individuals. Fractures of bones not followed by sarcomatous complications had occurred in two members of this group on previous occasions. It has been claimed that a second injury to a bone, which sustained a trauma many years previously, may activate the primary tissue reaction and change it into a sarcomatous response (Schosserer; and Fraenkel).

The medico-legal decision concerning an allegedly traumatic osteogenic sarcoma is often difficult, because of defective data on which to base a reliable evaluation. An osteogenic sarcoma becoming manifest within a few days to several weeks after the trauma is in all probability not causally related to this event, unless it can be shown that the trauma affected a prepared soil (brown tumor, osteitis fibrosa and constitutional osseous fragility). Under such circumstances it is essential to decide if the trauma played only a minor role in the causation of the sarcoma, by furnishing the final stimulus to a tissue already endowed with malignant although temporarily quiescent qualities, or whether the trauma was of major importance, by causing such reactions in a pathological but benign tissue that a malignant transformation ensued.

A traumatic causation of an osteogenic sarcoma appears to be more likely when several months or years have elapsed before the malignant development becomes apparent. A causal relationship between the two events is suggested when the injury produces a larger hematoma, which is absorbed only gradually, and pain and local swelling persist into a period where the malignant character becomes definite. It is advisable to prepare roentgenograms from all injured bones, especially in cases of fracture, to exclude to some extent the presence of spontaneous fractures caused by the existence of a primary or secondary neoplastic process, or some other osseous pathology in the bone at the time of the "accident." Suspicion, in regard to the existence of a spontaneous fracture of this type in the absence of any definite evidence of a primary malignancy remote from the site of the fracture, should be entertained in all fractures affecting elderly individuals, in all showing an unexplainable delay in the

healing and consolidation of the fracture, or in those displaying a marked discrepancy between the severity of the trauma sustained and the site and type of fracture observed. It is important under such circumstances to exclude the presence of cancers of such organs which have a tendency to form metastatic deposits in bones (cancers of the breast, thyroid, stomach, prostate, and kidney).

A traumatic aggravation of a pre-existing osteogenic sarcoma must be considered as a distinct possibility. Kolodny stated that if a tumor appears soon after a trauma, it is probable that the neoplasm existed long before the injury, and the latter merely led to its discovery or to an exacerbation of its growth. Such an effect appears to be especially likely in the case of central sarcomas, in which a trauma may produce a break in the surrounding bony shell of the tumor or cause a tear in its periosteal limitation, greatly facilitating the local and general dissemination of the neoplastic tissue. It is for this reason that the performance of osteotomies for diagnostic purposes is considered as contraindicated (Behring; Ewing; and Richards and Singleton) in cases of suspected, centrally located, osteogenic malignancy.

There remains finally the question whether or not the localization of a metastasis of a primary cancer from some organ other than the bone at the site of an old fracture should be considered as a traumatic aggravation of a malignant disease (Barret; and Fenster). It is still a controversial issue whether a fracture represents a locus minoris resistentiae for the colonization of cancer cells. It is often argued in such cases that the preceding fracture was not an accidental one but a spontaneous one, caused by the presence of neoplastic processes at the site of the fracture at the time of the alleged accident. This attitude has been maintained even in the face of negative roentgenograms taken soon after the accident, as it is a well-known and definitely established fact that an extensive neoplastic involvement of a bone may exist, which may not be shown in roentgenographic examinations (Fenster). Medico-legal decisions should be guided by the following considerations: An aggravation of a neoplastic disease can be conceded only when the formation and localization of the metastasis at the site of a previous injury to a bone involves an area of vital importance thereby hastening the death of the individual. Whenever such a constellation does not exist, it is justified to regard the metastatic localization allegedly determined by the trauma as one of the many possible sites of normal metastatic spread, exerting no appreciable influence upon the ultimate course of the disease.

8. NOTOCHORDAL TISSUE

Chordomas originate from rests of the chorda dorsalis (notochord), which is of ectodermal origin and represents a specific embryonic tissue around which the mesodermal vertebral spine develops, and which remains preserved normally in the center of the intervertebral discs (nucleus pulposus). Rests

of this soft, jelly-like tissue may persist for a prolonged period at both ends of the spinal column in the occipital and coccygeal regions, rarely in other parts of the spine (Stewart and Morin; and Simon). It is from these vestigial foci that neoplastic formations usually originate. The presence of an embryonal anlage is considered, therefore, by some investigators as an essential requirement for the development of chordomas during later life (Fischer-Wasels). While occupational influences have not been incriminated as contributory factors in the genesis of these neoplasms, trauma has been accused of acting in such a role in several cases.

Peyron and Ardouin asserted that one-fifth of the chordomas observed had a traumatic genesis, whereas Andler and Schmincke noted that 35 per cent of these tumors were traumatically conditioned. Meyermann found, while reviewing 169 cases of chordoma, that a traumatic history was recorded in 14 instances (8 per cent). Roussy considers such claims unlikely, and Ewing pointed out that the conditions of origin as well as the long latency period do not favor a traumatic genesis of chordomas. Güthert expressed a similar opinion. The following citations may serve as an illustration of the traumatically conditioned chordomas:

Stanton reported a chordoma of the coccygeal region in a man, 62 years old, following a fall on the edge of a wagon-box, by which he hurt the base of the spine. The region was painful for a few days. Six months later the traumatized area became sore, and a swelling appeared 18 months after the accident. A sacro-coccygeal chordoma was removed 2 months afterwards. In a second case of allegedly traumatic chordoma, observed by the same investigator, a man, 35 years old, had sustained a fall on the head four years previous to the development of cerebral pressure symptoms (slowed mental reactivity, occasional vomiting, and headaches). A spheno-occipital chordoma was removed from the right temporo-frontal region. Since an antecedent trauma was noted in a great number of cases of chordomas reported by other investigators, Stanton concluded that it was reasonable to assume that, in some cases, trauma may be the exciting factor acting on an aberrant rest of notochordal tissue. Richards and King concluded, from the prevalence of chordomas in males, that trauma may play some role in the etiology of these tumors.

Peyron and Mélissinos, who collected the cases of sacro-coccygeal chordomas with an "incontestable" traumatic history, noted that the occipital chordomas which are usually more benign than the coccygeal ones, showed a traumatic relation less often than the latter ones. These investigators found records of 14 cases of sacro-coccygeal chordoma in which the available data indicated a traumatic causation. The latency period varied from two months to 20 years, but was, in 8 out of 9 cases in which this information was given, less than two years. The age of the individuals, which ranged from 22 to 78 years (58, 26, 54, 22, 56, 45, 49, 32, 39, 68, 78, 32, and 44), did not support, according to Peyron and Mélissinos, the assumption that an embryonic anlage with neo-

plastic potentialities represented a significant and essential factor for the production of chordomas. The trauma was thought to release the normal pressure from the intervertebral discs, and thus incite the dedifferentiation of the chordal tissue resulting in tumor formation. A traumatic causal factor existed, according to these investigators, in 23 per cent of the recorded cases of chordoma.

It is obviously very difficult to evaluate the possible or potential role which a trauma may exert in the genesis or upon the development of a chordoma, as these neoplasms are not only rare, but also inaccessible to direct observation. Their slow growth and long latency period complicates still further any decision on the traumatic origin of these tumors. It may be possible that a trauma does have some influence upon the realization of the neoplastic potentialities possibly possessed by the small aberrant vestiges of chordal tissue, frequently found in the occipital and coccygeal regions. A traumatic break in the normal confines of such formation may be followed, for instance, by a luxuriant growth into the adjacent tissue.

Ribbert attempted, according to Dürck, to produce these neoplasms experimentally by stabbing into the intervertebral discs of rabbits. Chordoma-like proliferations of the cells of these organs resulted, but regressed spontaneously after some time. The observation, while negative as to true tumor formation, suggests that the presence of an embryonic anlage may not be absolutely necessary as a focus of chordomatous growth.

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VIII

OCCUPATIONAL AND ACCIDENTAL TUMORS OF THE EYE AND ITS ADNEXAE

THE formation of benign and malignant neoplasms of the eye and its adnexae (eyelids, lacrimal organ, conjunctiva, and orbital tissue) on the basis of normal occupational and accidental factors has found so far scanty attention, in spite of the fact that the eye and its associated organs are exposed readily and frequently to the effects of exogenous agents of various nature. Occupational carcinogenesis of the ocular organs is apparently not rare and deserves for this reason more consideration than it has received heretofore.

1. CHEMICAL AGENTS

A. Inorganic Chemicals: Arsenic

The occupational exposure to white arsenic and other arsenicals has given rise to the development of papillomatous warts and cancers of the eyelids in workers of various metallurgical and chemical operations (smelting and refining plants of arsenic, lead, copper, zinc, silver, and iron ores; and manufacture of arsenicals, such as emerald green, Paris green, and lead arsenate) (Hunter; and Kennaway). The contact with the arsenic or arsenical is usually in the form of dust, which settles on the exposed parts of the skin of these workers.

B. Organic Chemicals (Tar, Pitch, Crude Oil, Lubricating Oil, and Paraffin)

An excessively high incidence of ocular malignancy (3 to 4 times the normal ratio) was found to be present in workers exposed to tar, asphalt, pitch, mineral oils, and similar products, according to the statistical studies Lane conducted on a series of 1,000 cases of cancer of the eye and its adnexae, collected from 22 eye clinics in the United States and Canada, from private records of many eminent ophthalmologists, and from the medical services of large industrial plants producing chemicals, oils, carbon products, and gas, and from the automobile industry. The high incidence of these neoplasms among carpenters, observed by Lane, is attributed to their handling of creosoted shingles, and is not considered a result of frequent mechanical injuries sustained by members of this occupational group. These observations agree with similar ones recorded by American and European investigators (Martin; Legge; Hessberg and Bär; and Story).

Legge noted in a treatise on the epitheliomatous ulcerations in industry in

1922 that pendulous pitch warts with slender pedicles are frequently observed on the eyelids, especially the upper ones, of pitch workers in the Cardiff region. In a series of 80 cases with occupational epithelioma due to pitch, tar, or paraffin, twelve tumors were located on the eyelids (pitch 9, tar 2, and paraffin 1). Hessberg and Bär reported the occurrence of a cornifying squamous-cell carcinoma on the lower lid of a briquette worker, who was 69 years old and had been in contact with pitch for 7 years as a mixer. A similar case of multiple papillomata and carcinomas of the face, especially involving the eyelids, of a pitch worker only 19 years of age was recorded by Zweig (1909). Leclercq and Cordonnier cited the occurrence of an epithelioma in the inner corner of the eye extending to the upper lid in a French soldier, who was employed as prisoner during the war for a period of three years in a briquette plant, and was injured by fragments of pitch in the region of the internal corner of the eye, the lower lid, and in the skin below the eyebrows. The resulting lesions did not heal but grew into ulcers, which were diagnosed histologically as epitheliomas of the spinous-cell type. In a study of the anatomical distribution of occupational cancers, Kennaway listed among 110 pitch cancers 12 as situated on the eyelids or affecting the eyes, and among 34 tar cancers 2 as located on the eyelids. Nicolas, Lacassagne, and Rousset mentioned the presence of pedunculated soft papillomas on the eyelids of a tar worker. In a survey of the cutaneous papillomas among patent fuel workers in England, Downing found that among 107 cases of pitch papillomas and epitheliomas studied, 5 papillomas and one epithelioma affected the orbit and 13 papillomas the eyelids. The epithelioma started in the cornea of the eye. The occurrence of a rapidly growing warty tumor in the region of the left inner angle of the orbit in a tar and pitch worker, 33 years old, was recorded by Goulden and Stallard. Seven years later the same individual developed a small wart on the left upper eyelid, which was shown to be a squamous-cell carcinoma. A traumatic type of pitch cancer of the eye was observed by von Berger, who reported the development of a nodule on the limbus of the cornea together with iritis in a coal porter, who had been injured in the eye by a splinter of tar which was lodged in the cornea. The neoplasm was a cornified squamous-cell carcinoma. A somewhat similar case was placed on record by Milan and Garnier, who noted the appearance of a spinous-cell carcinoma of the lower lid in a gas house worker several weeks after he had sustained a burn with tar in this location. Blum and Bralez found an ulcerated cornified squamous-cell carcinoma in the inner corner of the eye near the nose in a gas plant worker, 33 years old, after having been burned at this site by hot tar. O'Flynn and Twigg observed the development of a melanocarcinoma in the conjunctiva of a sailor, 19 years old, two months after liquid pitch had splashed into his face, and into the lower and outer part of the conjunctival sac. Whereas the pitch was removed from the eye soon after the accident, an ulcer remained, which assumed malignant qualities.

The causation of cancer of the eyelid through an occupational exposure to crude oil was reported by Sharp, who noted that in many histories of a series of 48 cases of malignancy of the eyelid mention was made of the fact that the face and eyelids had been rubbed with hands soiled with various coal tar products, such as lubricating oils and greases. The cancer appeared in one of these cases two years after a burn with hot grease, producing an ulcer which did not heal. In a second case of this group the individual developed 18 cancers located in the face and eyelids, after having used for a period of 40 years crude oil and gasoline in cleaning stoves.

2. PHYSICAL AGENTS

A. Radiating Energy (Solar and Ultraviolet Rays, Roentgen-Rays, and Radioactive Substances)

Conforming with the observation that an excessive occupational exposure to solar rays is responsible for a high incidence of cancer of the skin, Lane found, through a statistical analysis of 1,000 cases of cancer of the eye and its adnexae, that workers exposed to sunlight, such as farmers and outdoor laborers exhibit a marked incidence of ocular malignancy. A similar conclusion was reached by Sharp, who noted that the second most frequent cause of cancer of the eyelids was represented by solar rays. Martin commented on the fact that the exposure to solar rays is one of the causes of malignancy of these organs.

These clinical observations have received substantial support by the results of experimental studies on the carcinogenic action of solar and ultraviolet rays upon the skin (Roffo; Huldschinsky; Putschar and Holtz; Wahlgren; Beard, Boggess and von Haam; and Hueper). Roffo reported that rats exposed to intense solar irradiation for a period of seven months developed carcinomas and sarcomas of the exposed and least protected parts of the skin, chiefly the eyes and the ears. Similar results were obtained when rats were subjected to ultraviolet radiation of the wave lengths between 1,800 Å and 3,400 Å. Malignant tumors (sarcomas) of the eyes were produced in 26.25 per cent of the animals, while the eyelids were frequently involved by sarcomas and carcinomas. These results have been confirmed by Putschar and Holtz; Wahlgren; Beard, Boggess and von Haam; Hueper; and Huldschinsky in experiments with mice and rats. The orbital sarcomas observed in these cases originated from the conjunctiva.

Finally, Lane listed four cases of ocular cancer (1 sarcoma, 3 carcinomas) as of occupational genesis of roentgen-ray type among 1,000 cases surveyed.

B. Physical Trauma

Pseudotumors. Penetrating as well as dull injuries of the eyeball may result occasionally in the formation of pseudotumors, such as traumatic epithelial

implantation cysts in the iris (Hudelo; Moore; and Bonnet and Paufique) and heterotopic cancellous ossifications in the vitreous body.

True Tumors. Among the various malignant neoplasms affecting the eye, the retinoblastoma can be absolved from having any relation to a traumatic genesis, as these tumors appear, as a rule, at an early age (before the eighth year) and exhibit a definite congenital and sometimes hereditary quality, showing a certain predisposition for the Jewish race. There is a single case of an allegedly traumatic causation of a retinoblastoma on record, which was reported by Patwardhan, who observed the development of such a malignancy in the eye of a boy, 6 years old, who had suffered six months previously a perforating injury to the eyeball, followed by a large hemorrhage and loss of vision.

The possibility of a traumatic origin of the most frequent ocular tumor, the choroidal melanosarcoma, is still a controversial matter. There exists a great deal of evidence indicating that an injury to the eye plays a certain causal role in the development of these neoplasms. Winterstein, who studied 90 cases of choroidal sarcoma reported as traumatic, conceded the possibility of a causal relation between the accidental injury and the cancerigenesis for only four of these cases. Verhoeff analyzed over 300 cases of ocular melanosarcoma without finding a reliable traumatic history in a single instance. Bancroft noted that in 126 cases of choroidal melanosarcoma studied by him nine histories mentioned a preceding trauma to the affected eye, but the relationship between the ocular injury and the neoplasm was admitted to be incidental in all instances. Benedict surveyed 1,439 cases of ocular tumors and found a traumatic history in 7.14 per cent of the 126 melanotic neoplasms contained in this series. The trauma was an incidental event in these cases, in the opinion of Benedict.

There exist a great number of individual case reports of allegedly traumatic melanosarcomas of the eye which deserve serious consideration (Coleman; Kipp; Ball and Lamb; Nitsch; Chance; Holloway; Stieren; Kalt; Pfingst; and Fenster). Coleman recorded a sarcoma of the iris eight months after an ocular injury sustained during the explosion of a gun cap. A sarcoma of the eye, becoming manifest three years after an injury to the eye, which resulted in a continued inflammation of the traumatized organ, was noted by Chance. A melanosarcoma of the ciliary disc appearing in a man, 40 years old, three months after sustaining an injury to the limbus by a fragment of wood, was reported by Kipp. Holloway recorded a melanocarcinoma of the choroid in an individual, 23 years old, following a hammerblow to the eye received three years before, leaving an impairment of vision. Bonnet and Paufique observed the appearance of a melanosarcoma in the eye two years after being injured by a severe blow, which resulted in the separation of the retina from its base. The development of a melanosarcoma in a shrunken, atrophic eyeball, previously traumatized, was mentioned by Fischer-Wasels.

The age range of these traumatic sarcomas of the eye is very wide, starting with the age of seven (Nitsch) and extending into the senile period. The incidence of the traumatic sarcomas increases with advancing age.

Ewing; Knox; and Verhoeff, who do not concede a traumatic causation of choroid melanosarcomas, have raised the following objections against such a relationship: The eye is frequently injured, even physiologically, every day many times, without responding to such traumatization with the development of melanotic neoplasms; such tumors are relatively rare; and numerous severe injuries to the eye, involving the melanin carrying constituents and causing prolonged and permanent pathological changes in the eye, have not been followed by neoplastic responses of this type, militating against the assumption that a trauma may activate a predisposing and preexisting anatomical anomaly and congenital malformation in the eye. Any dogmatic, though perhaps scientifically permissable, attitude in such a matter cannot overcome the fact that our knowledge of the causal factors underlying many cases of malignancy is highly defective or non-existing. It is rather negligible for this reason that the traumatic production of choroid melanosarcoma has not been accomplished experimentally. The circumstantial evidence presented by some cases is such that a causal interrelation between the preceding ocular trauma and the occurrence of the choroid melanosarcoma must be acknowledged in exceptional cases from a medico-legal standpoint. It is highly improbable that even in these cases the trauma represents the main or only cause of the tumor.

In adjudging the relation of the site of the injury to the location of the tumor consideration must be given to the fact that a trauma to the eye may cause pathological changes of the eye in places remote from the region directly injured. It is, therefore, not absolutely essential from a medico-legal standpoint that the sites of trauma and tumor coincide.

A few reports mention the traumatic genesis of malignant tumors in adnexal organs of the eye. The development of a sarcoma in the lacrimal caruncle one month after an accidental burn by a lighted cigarette was observed in a boy, 7 years old, by Alexiades. Pincus reported the appearance of a cylindroma of the lacrimal gland in a boy, 14 years old, whose lid had been hit three months previously with a board, causing a hemorrhage into the substance of the lid. This investigator stated that nine similar reports concerning the development of a cylindroma or of a mixed tumor in the orbital tissue of a previously injured eye were found in the literature.

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IX

OCCUPATIONAL AND ACCIDENTAL TUMORS OF THE NERVOUS SYSTEM

1. GENERAL ETIOLOGICAL ASPECTS

THE occurrence of benign or malignant tumors of the nervous system resulting from some injurious occupational activity is not known, according to the data available at the present time. The prevalent theoretical conceptions as to the causative factors active in the cancerigenesis of the nervous system, especially the brain, are not favorable to a serious consideration of such interrelations, as they are based mainly upon the theory of *Cohnheim* (misplacement of embryonic nerve tissue and tissue malformations) (Cushing; Bailey and Cushing; Ostertag; Fischer-Wasels; Globus; Henschen; Dietrich; and Gruber). Apart from the fact that the alleged embryonic character of the glial foci, which are claimed to represent the potentially blastogenic anlagen, has been challenged with good cause by other investigators, the successful production of cerebral gliomas by the action of recognized chemical carcinogens, accomplished in recent years, provides additional evidence in support of the conception that other factors, especially exogenous chemical agents, than embryonic cellular foci may be involved in the causation of neoplasia of the nervous tissue. Such a possibility deserves serious attention for several additional reasons. The experimental carcinogenesis obtained with various chemicals in different organs (skin, lung, liver, and bladder) has shown definitely that embryonic rests are neither involved nor essential for the development of these malignant tumors, and that they do not play any important role in the production of the great majority of the known occupational neoplasms. Toxicological studies have demonstrated that a great number of chemical agents (mercury, lead, manganese, arsenic, aniline and other aromatic nitro- and amino-derivatives of benzol and naphthalene, carbon monoxide, *hydrogen sulfide, carbon disulfide, ethylene glycol dinitrate, and nitroglycerin*) exhibit a definite and even a marked affinity for the tissues of the nervous system, and are the cause of more or less extensive degenerative as well as regenerative and reparatory lesions (Bumke and Krap). Inasmuch as some of these chemical agents listed exhibit definite carcinogenic properties in other organs than the brain, it must appear peculiar that none of these chemicals, frequently causing occupational poisoning of acute and chronic type, should ever have caused a cerebral tumor, especially if an activation of the dormant neoplastic potentialities of the numerous embryonic rests, said to be scattered throughout the brain, would represent the only action necessary. If physical

and chemical stimuli, in addition to a special disposition of certain nerve cells and regions, are mainly responsible for the genesis of cerebral blastomas, as claimed by Beneke, the possibility must be conceded that stimuli of an occupational origin may play this role in some cases.

2. EXPERIMENTAL PRODUCTION OF CEREBRAL TUMORS

The first attempts made to produce experimentally neoplasms of the brain with the aid of carcinogenic hydrocarbons failed completely. Necrotic lesions of the brain only resulted when small pieces of gauze saturated with tar were placed on the surface of this organ in rabbits (Roussy, Oberling, and Raileanu). In a subsequent set of experiments Oberling, Guérin, and Guérin implanted benzpyrene crystals into the brain of rats without obtaining any proliferative glial response. The intracerebral injection of this substance in an oily medium resulted in the development of pituitary adenomas, but failed in the production of glial neoplasia. Similarly negative experiments were conducted by Peers, who injected 1.2.5.6-dibenzanthracene (5 per cent in lard) in solution and implanted this chemical in the form of a cholesterol pellet into the brain of albino mice. None of these animals exhibited any neoplastic reaction of the nervous tissue after 296 days. The implantation of cholesterol pellets containing 1.2.5.6-dibenzanthracene into the brain of mice was negative after 8 months (Ilfeld).

Weil succeeded when he injected certain carcinogenic chemicals into the brain of rats. One out of six rats injected with a solution of 1.2.5.6-dibenzanthracene in lard developed an intracerebral squamous-cell carcinoma, while three out of five rats injected with a saline solution of styryl 430 [2 (p-aminostyryl) 6-p-acetylaminobenzoylaminoquinoline methoacetate] developed glioblastoma multiforme, ependymoma, and meningioma, respectively. An overgrowth of Schwann's cells and fibroblasts, resulting in a reaction comparable to neurinoma of the cranial nerves in the human brain, was found where the dye came into contact with cranial or spinal nerve roots. None of the rats inoculated with 1.2.5.6-dibenzanthracene showed any evidence of a pituitary adenoma, in contrast to the observations made by Oberling, Guérin, and Guérin.

Rats injected with styryl 430 exhibited a neoplastic transformation of the pars nervosa and glandularis of the hypophysis. Cook; and Seligman and Shear were successful in causing cerebral tumors by the experimental introduction of cyclic hydrocarbons of carcinogenic quality into the brains of animals. Shear obtained, by implantation of methylcholanthrene-cholesterol pellets into the brain of mice, cerebral tumors in 13 out of 20 animals. All of them were gliomas. Peers reported subsequently that of 99 rats implanted intracerebrally with methylcholanthrene-cholesterol crystals, 32 developed tumors of which 15 were derived from nervous tissue elements.

3. TRAUMA AND TUMORS OF THE NERVOUS SYSTEM

A. Brain Tumors

Although ordinary occupational activity has not played any role so far as an alleged cause of tumors of the nervous tissue, mechanical and psychic accidental trauma has been incriminated in this respect in numerous instances, and on this account has been the subject of many lively scientific controversies and medico-legal disputes. The importance of a possible relationship between trauma and neoplasm of nerve tissue is enhanced by the fact that the great majority of cerebral blastomas have an unfavorable prognosis.

The case histories of brain tumors contain data concerning the occurrence of a cranio-cerebral injury preceding the onset of the symptoms of a neoplasm. The absolute frequency with which such an event is recorded in the series reported by the various investigators depends greatly upon the inquisitive diligence exerted and the amount of discrimination displayed in the individual case. Müller contended that 70 per cent of all cerebral tumors were of traumatic origin. A history of a head injury was elicited in 40 per cent of the cases observed by Beneke as well as Nussbaum, in 30 per cent of those recorded by von Monakow, in 15 per cent of those studied by Frazier, in 12 per cent of the 115 cases investigated by Walter, in 8.8 per cent of the 1,086 cases collected from the literature by Adler, in 4.8 per cent of the 431 cases analyzed by Parker and Kernohan, and in 2.6 per cent of 150 cases by Cox. The peak in the frequency of this relation was found in individuals from 40 to 60 years of age (Adler). Men were involved more often than women [51.8 to 83.6 per cent in men (Adler), 75 per cent in men (Thiem)].

The great majority of investigators do not recognize the existence of a causal connection between a trauma and a cerebral tumor. They argue that the trauma is either a coincidental event, or may have called attention to the presence of symptoms from a cerebral neoplasm or accentuated these manifestations, as it is claimed a brain containing a tumor is more likely to be injured by a blow than a normal brain. Some of these investigators concede that a cranio-cerebral trauma may act in the role of a realization factor, that is, it may activate a preexisting, congenital, dysontogenetic, embryonic, glial focus possessing dormant blastomatous potentialities (Cushing; Bailey; Ostertage; and Bruns), and thus precipitate the development of a cerebral tumor, especially as areas of the central nervous system containing simple malformations are believed to possess an enhanced reactivity because of traumatic influences. A smaller group of investigators has advanced pertinent evidence supporting the contention that, in some cases, a trauma to the brain may result in the production of glial lesions, which may assume ultimately malignant qualities after a varying period of time (Beneke; Nussbaum; Marburg; Bramwell; Oppenheim; von Monakow; Neubürger; Richter; and Moersch).

The experiences gained by the World War do not seem to have helped in

deciding this issue either way. While the objectors pointed to the absence of an increase in the incidence of brain tumors during the years which have passed since the end of this event (Parker and Kernohan; and Wilson), Scheid stated that 4 cerebral neoplasms were found per 10,000 soldiers with war injuries to the brain, whereas 5.3 neoplasms were observed per 1,000,000 gun shot wounds involving other organs.

Statistical analyses scarcely represent a suitable and propitious approach to a final solution of this problem. A detailed investigation of the relative merits of the evidence presented in support of the various theories of cerebral cancerigenesis is indicated, as such a procedure may help in elucidating the role a cranio-cerebral trauma possibly may play in the causation of such neoplasms.

The dysontogenetic theory, which assigns to a trauma at most a purely secondary and minor role of a realization factor, is based chiefly upon two observations. There exists a causal relationship between congenital malformations of the nervous system and the occurrence of gliomas of the brain. This is demonstrated most strikingly by two diseases of the nervous system, both being observed in young individuals and both characterized by the presence of congenital developmental disturbances in the central or peripheral nervous system as well as in other organs. In tuberous sclerosis the brain contains heterotopic and histiotopic glial foci (gliosis), exhibiting a cellular pattern similar to that existing in the infant's brain (Globus) and showing an irregular arrangement of the fibrils, an excessive size of the individual cells and focal conglomerations, and band-like arrangements of glial cells. The multiple heterotopic glial foci and nodules occurring in the medulla of the hemispheres and in the wall of the ventricles along the arteria terminalis are dysplasias with blastomatous components (Neubürger), and some of them develop into spongioneuroblastomas. In addition to these tissue abnormalities in the central nervous system there occur solitary or multiple malformations of blastomatoid or blastomatous character in other organs [rhabdomyoma of the heart (Steinbiss; Vogt; and Hueper), adenomas of the kidney, liposarcomas, and adenomas of the sebaceous glands]. The second disease is represented by neurofibromatosis, which mainly affects the peripheral nervous system and is characterized by the formation of multiple neurinomas of the peripheral nerves, but which not infrequently is associated with the development of heterotopic glial foci and gliomatosis of the brain. This disease is often accompanied by disturbances in the pigmentary metabolism, and occasionally by abnormalities in the formation of bones. As tuberous sclerosis may be observed during the first few months of life, exogenous influences have apparently no essential part in the etiology of these diseases, but disturbances in the normal development of the fetal ectoderm are the causal factors underlying the production of the cerebral tumors. The familial, hereditary character of neurofibromatosis, its frequent combination with dysontogenetic formations in other organs (multiple meningiomas and adenoma sebaceum), and the multicentric character of the lesions

exclude practically any appreciable influence of a trauma upon the causation or course of this disease (Harbitz; Schröder; Enokow; Foerster and Gagel; and Turner and Gardner).

With this definite evidence available, it was very suggestive to extend the theory of a dysontogenetic genesis of cerebral neoplasms from this small and rare group of disorders to the cerebral blastomas in general, reviving a hypothesis of Cohnheim, which had fallen into disrepute to a great extent in recent years. The observations which provided the apparent basis for this conception consisted in the demonstration of foci of "embryonic" glial cells in certain definite locations in the brain of babies (Ranke). As the site of some cerebral tumors conformed with the location of some of these foci, it was argued that the persistence of such embryonic glial foci, representing germinal centers of medulloblasts, beyond the period of the cerebral maturition (Roback and Scherer) would furnish the embryonic anlagen with neoplastic potentialities from which subsequently gliomas might arise. While it may be conceded that certain tumors, such as medulloblastomas, originating from the roof of the fourth ventricle, or the rest of the craniopharyngeal duct, may support such a working hypothesis, such an explanation does not fit the great variety of glioblastomas (Weil). This investigator pointed out that any attempts to construct germinal centers for these neoplasms within the adult brain were doomed by the mere fact of their ubiquitous nature. No binding evidence exists concerning the actual presence of neoplastic potentialities in these groups of undifferentiated glial cells, which are morphologically very similar to the growth centers found in the neighborhood of vessels in gliomas, and which are said to account for the not infrequent multicentric development of these tumors. Tuthill, who made a special study of these glial formations occurring in the brains of young babies, emphasized the fact that it is not possible to indicate whether consequences attend incomplete or prolonged cerebral growth.

Beneke, on the other hand, pointed out that developmental malformations in the brain do not result, as a rule, in the subsequent appearance of malignant blastomas, but of benign formations (dermoid, epidermoid, and cholesteatoma), which do not exhibit any malignant potentialities.

Recent investigations have extended a much more serious challenge to the supporters of the dysontogenetic theory of cerebral oncogenesis, by denying the embryonal character of these glial conglomerations and assigning to them a secondary reactive nature (Schwartz; Wald; and Beneke), thereby removing the very foundation of the embryonic theory. It is contended by these investigators that the glial proliferations found in the brain of new-born and young babies do not represent manifestations connected with the maturition of this organ, but are glial responses to cerebral injury sustained during birth. The frequent presence of multiple cerebral hemorrhages in the brain of newborn babies and the demonstration of glial cicatrices, scleroses, cysts, poren-

cephaly, and idiocy as the late results of birth trauma, is mentioned in support of these claims, the partial correctness of which had to be conceded by Wohlwill, who is an adherent of the dysontogenetic dogma.

These observations have reduced greatly the value of a powerful argument advanced heretofore in favor of Cohnheim's theory, that is, the high incidence of medullo-glioblastomas among children, which was attributed to blastomatous transformations of congenital glioblastic anlagen. Beneke claimed in contradistinction that regenerative glioses, representing sequelae of a cerebral trauma sustained during birth, are the basis for this phenomenon. The evidence thus far presented indicates that embryonic developmental anomalies are the blastogenic anlagen for a relatively limited number of cerebral neoplasms, but have no proven or probable relation to the great majority of these tumors. Some circumstantial evidence even suggests that focal glial proliferations, resulting from birth trauma, may occasionally assume such a role.

Before the conception of a possible transition of reactive, regenerative, and reparatory glial proliferations into neoplastic formations is given serious consideration in connection with traumatic episodes, a detailed survey of the ultimate outcome of cerebral glial reactions of various origin is essential. Meyer and Cook reported the presence of a diffuse gliosis of the white matter of the brain in mental defectives. These investigators stressed the absence of any developmental errors and of immature or blastomatoid characteristics of the proliferating glial cells, such as observed in the glioses associated with tuberous sclerosis and von Recklinghausen's disease. The glial proliferations in mental defectives were attributed by Meyer and Cook to abnormalities in the vascular pattern of the brain, causing a locally deficient oxygenation of the white matter, which in turn resulted in the glial proliferation. Marked and especially perivascular glial reactions are observed in connection with certain infections of the brain (epidemic encephalitis) and with numerous chemical poisonings (mercury, lead, and manganese). No data are available as to the occurrence of neoplastic sequelae from such conditions.

It is known that in multiple sclerosis, a disease of the central nervous system characterized by multicentric glial foci in the spinal cord and by gliosis of the brain, multiple, small, cerebral gliomas may occur (Müller). Syringomyelia (spinal gliosis with multiple cavitation of the spinal cord and medulla oblongata) is accompanied by the occurrence of small, tumor-like glial nodules within the gliotic areas located in the grey matter, and occasionally multiple small gliomas in the brain exhibiting a diffuse gliosis (Müller). Since the etiology of multiple sclerosis and syringomyelia is highly controversial (for multiple sclerosis an infectious origin and chronic lead poisoning have been favored recently, and for syringomyelia surgical trauma sustained at birth has been accused), the value of this evidence is more of a general and circumstantial character, but favoring the existence of interrelations between reactive glioses and gliomatoses of the brain.

It appears essential for the establishment of more or less definite relations between the anatomical effects of a cranio-cerebral trauma and the subsequent appearance of a gliomatous tumor of the brain, to present the acute and late effects of such episodes upon the nervous tissue, as they form the basic lesions from which the alleged neoplastic developments ensue. A sharp, penetrating trauma and a dull injury (commotion and concussion) of the brain may result in laceration of the nervous tissue, in small (petechial) or large hemorrhages into the brain substance, and in tears and hemorrhages of its membranes. These direct traumatic effects are followed by acute reactions in the circulation of the blood and cerebro-spinal fluid, which may be caused in part by functional spasms of the vascular walls (Beneke; and Nussbaum). Because of these circulatory disturbances an edema of the brain and focal ischemia with secondary necrosis of the nervous substance develops (Winkelman and Eckel; Meyer; Wohlwill; Neubürger; Rosenhagen; and Courville and Kimball.)

The acute traumatic alterations in the cerebral structure are followed by reactive, regenerative, and reparatory changes of the glial tissue, the fibroblastic elements, and the meningeal membranes. These secondary manifestations may persist and progress for many years after the trauma (Winkelman and Eckel; Rand and Courville; and Neubürger). The secondary anoxemia, representing a frequent aftermath of the traumatic circulatory disturbances of the brain (hemorrhage and congestion), results in the development of chronic degenerative alterations of ganglion cells, especially in the basal nuclei, and in the proliferation of glial cells and meningeal tissues. Local glial accumulations appear around small foci of cerebral softenings and cyst formations. These small glial cicatrices give rise to the appearance of crater-like retractions at the tip of the gyri in cases of cerebral concussion (Esser). Larger foci of destruction of nervous tissue are transformed gradually into cysts with glial walls or into fibroglial scars (Neumann; Adler; and Weaver), often containing old blood pigment.

Whenever the trauma is severe and causes a prolonged post-traumatic unconsciousness, the secondary glial reaction may be much more marked and generalized throughout the brain and accompanied by the appearance of small glial nodules. Superficial cortical lesions and arachnoid hemorrhages give rise to the formation of meningo-cortical adhesions, which may cause the appearance of a traumatic epilepsy, a condition elicited, also, by traumatic depression fractures of the skull. Arachnoid hemorrhages may result in a cellular thickening of this membrane and in the formation of arachnoid cysts (Weaver). Subdural and epidural traumatic hemorrhages become organized gradually and may cause a thickening of the periosteum of the bony skull, persisting for months and years after the accident. The extent and type of the anatomical lesions produced in the brain by a trauma do not always reflect the severity of the injury. Apparently minor injuries may be followed by extensive and marked changes in the substance of the brain. Such lesions may be relatively

slow in development and may be progressive in course, thus giving rise sometimes to the first neurological symptoms (headache, giddiness, vomiting, and mental changes) several weeks after the trauma, after a preliminary period of relative well being (Wilson). The development and growth of such disseminate glial islets are apparently responsible for the progressive scattered deterioration of the brain structure frequently seen in boxers (Martland). Wilson considered the development of the post-traumatic, disseminate, glial sclerosis of the brain not as the expression of a normal reparatory response, but as the result of an activation of a previously dormant infection of the brain by the trauma.

The reactive, post-traumatic, diffuse glioses are of special significance in regard to the alleged transition of glioses into gliomatous proliferations, as they may assume a character, which makes their differentiation from gliomatous growths very difficult or impossible (Bonome; Cassirer and Levy; and Moersch). Bonome attempted to establish definite and reliable differential diagnostic, morphological criteria for the distinction between glioses and gliomas. Glioses are, according to Bonome, glial proliferations without limitation, which do not exhibit any marked tendency to spontaneous hemorrhages and necroses, which contain, as a rule, ganglion cells originally present in the gliotic part of the brain and consist of glia cells of more or less normal character, producing an increased amount of fibrils.

Gliomas are glia cell proliferations with limitary properties, which show a tendency to hemorrhages from newly formed vessels and necroses. They do not contain, with rare exceptions in tumors of congenital, mixed nature, any ganglion cells. They are composed of glia cells of varying degree of differentiation and anaplasia (polymorphism, hyperchromatism, multinuclearity, atypical mitoses, and rosette formation), which produce a small amount of fibrils.

While these differential-diagnostic criteria may be of value and help in some cases, they have proved to be inadequate in others. Cassirer and Levy reported a case which was originally diagnosed as a diffuse traumatic gliosis, and was later shown to be a glioma. Moersch described two similar cases which represented in his opinion transitional forms between a post-traumatic diffuse gliosis and a traumatic gliomatosis. Although some investigators still maintain that these post-traumatic glioses represent the glial equivalent of a traumatic cutaneous keloid, others (Moersch; Neubürger; Merzbacher; and Ewing) concede the possibility that a gliomatous gliosis may be a sequela of a craniocerebral trauma, developing from a local proliferation of capillaries and glia cells activated by nearby cerebral hemorrhagic areas.

While certain observations made in connection with some non-traumatic and traumatic reactive gliosis strongly suggest that a transformation of such glial hyperplasias into gliomatous proliferations is possible, the evidence available indicates, nevertheless, that such a development is an exceptional

one and that additional factors must be active to bring about this result.

It is therefore essential for the establishment of definite causal relations between a trauma and a cerebral neoplasm in the individual case to obtain anatomical evidence demonstrating the close local connections between the traumatic residues and the cerebral tumor. The following residues are of significance in this respect: scars in the skin of the head and changes in the bony skull and meninges (healed fracture, depressions, bony splinters, thickenings of periost, meningeal thickening, meningeal tears, organized meningeal hemorrhage, arachnoid cyst, and meningo-cerebral adhesions) above or opposite to the site of the tumor; fibro-glial scars with surrounding reactive cerebral gliosis, old blood pigment, cerebral cysts (former liquefaction necroses or hematomas), and foreign bodies (bullets and shell splinters) in close proximity, in direct contact with, or surrounded by the glioma. The intracerebral lesions may exist on the side previously affected directly by the trauma or may be found on the opposite side of the brain in the direction of the traumatic extension, being the sequelae of the countercoup (Adler; and Naville).

In the evaluation of these lesions proper consideration must be given to the fact that the significance of some of them regarding a traumatic origin is greatly limited, as identical changes may occur within or adjacent to the tumor as the result of the neoplastic growth. Spontaneous necroses and hemorrhages, often followed by cystic formation, are found rather commonly in gliomas, especially in the cellular types, and less often in the more mature fibrillar varieties [in 80 per cent (Karitzky)] (Doerr; and Schley). A perigliomatous increase of glia cells is a frequent normal feature caused by a direct compression of the cerebral tissue surrounding the neoplasm and being then only an apparent one (Karitzky), or representing a reactive gliosis (Singer), which may even involve parts of the brain remote from the neoplasm, and being the result of secondary circulatory disturbances or a response to the production of toxic substances from degenerating and necrotic parts of the blastoma (Agostini). Karitzky even doubted that the presence of scar tissue in a glioma was always indicative of a traumatic residue, as he observed, during the study of 133 cerebral tumors, in 2 cases scar tissue within the neoplastic tissue. As these scars occurred in close relation to necroses, Karitzky argued that these scars represented the cicatricial end results of primary degenerations of the neoplastic tissue. A growing blastoma may obliterate in the course of its progress many traumatic residues originally present in the brain.

A careful and thorough anatomical and histological study of the brain and its membranes and a cautious and discriminating interpretation of the observations made is essential in every case of alleged traumatic cerebral neoplasia, as clearly demonstrated by the considerations noted above. It is necessary for a reliable evaluation of a case to obtain the following additional data: a) The histological type of the tumor must be ascertained, as the proliferative activity of immature tumors (medulloblastomas-glioblastomas) is much greater than

that of mature gliomas (astrocytomas). The histological type and the size of the glioma must be proportionate to the interval elapsed from the time of the accident. Proper allowance must be made for the size of hemorrhages and necroses possibly present in the tumor mass. b) The site of the tumor is important in regard to the time of onset of neurologic symptoms, which depend on the size of the tumor, the occurrence of hemorrhages, and the environmental spatial conditioning (v. Monakow). These factors determine the relative length of the latency period, which may vary from 6 months upward to more than 14 years. Thiem stated that 5/7ths of all cases become manifest within the first three years after the injury.

The succession of pathological changes, which take place in the brain as the result of a trauma, makes it unlikely that an ultimate neoplastic evolution is the matter of a few weeks. It is more indicative of a traumatic etiology of a cerebral tumor, if the disappearance of the acute traumatic manifestations is followed by a more or less prolonged period, during which the injured individual is free from any symptoms compatible with an intracerebral neoplastic process (Scheid). The appearance of such symptoms within a few days to weeks following the injury favors a purely coincidental relation between the two phenomena, or may possibly indicate an activation in the growth activities of a preexisting tumor. While a traumatic aggravation of a preexisting glioma is possible (Wörth; and Windscheid) and has been observed, it is a well-known fact that gliomas display a marked tendency to hemorrhages, and glioblastomas may suddenly become dramatically manifest following such an episode after an entirely symptom free preliminary period or a time with rather mild and vague symptoms (fatigue and headache). An accident may not be the cause, but the result of a cerebral tumor (Parker and Kernohan). The symptoms produced by a cerebral tumor depend to a large extent upon its location in the brain (headache, dizziness, vertigo, attacks of petit mal, vomiting, convulsions, defects in visual fields, choked discs, mental deterioration, disorientation, irritability, attacks of transitory paresis, and change in pulse rate).

These observations and considerations must be coordinated and integrated with the following data which are essential before any competent opinion can be expressed as to the traumatic etiology of a particular cerebral neoplasm: 1. exact site of the injury; 2. exact type of the injury; 3. intensity of the trauma; 4. date of the accident; 5. date of the first symptoms and their character; 6. type of the subsequent development; 7. pre-accidental status of the individual (especially as to absence of any neurologic symptoms suggestive of a primary or secondary intracerebral lesion); 8. absence of a tumor history in any other part of the body (especially the lung); and, 9. absence of any hereditary predisposition to tumors of the nervous system (retinoblastoma).

Through the proper application of these criteria it is possible to eliminate a large number of brain tumors from the traumatic list. There remain a restricted number of cases, for which an important etiological role of a trauma

in a subsequent development of a cerebral glioma must be sustained. The following case reports may illustrate this point.

In a case recorded by Marburg, neoplastic proliferations of immature glia cells (bipolar spongioblastomas), originating from scar tissue, were found in the brain of a man who had been wounded five years previously, the bullet remaining lodged in the brain. A similar case was reported by Fischer-Wasels, who observed a glioma starting in a scar of the brain following a war injury by a shell splinter nine years previously.

Neubürger, who found three cases with gliomas among 21 brains of war veterans with brain injuries, related two cases which doubtless belong among the group of traumatic gliomas. The description of the first case deals with a soldier, 21 years of age, who had been wounded in the left parietal region and who developed soon after epileptiform seizures. Mental changes developed four years later and death ensued six years after the injury. The post-mortem examination showed beneath a meningo-cerebral adhesion at the site of the old wound a fibrous scar of the brain, surrounded by a zone of proliferating glia. This glial tissue was atypical in character (polymorphism, densely packed nuclei, and numerous mitoses), and was considered to be neoplastic. In the second case described by Neubürger, a soldier, 36 years of age, had been injured in the head by a splinter from a shell of a trench mortar. Since that event he complained about motor, mental, and psychic disturbances. Six years after the injury he developed a laevo-lateral hemianopsia pointing to a lesion in the occipital lobe, being the result of the action of a countercoup. At the necropsy performed soon afterward there were cicatricial cystic changes in the region of the old wound. A scar was found at the junction of the occipital-temporal lobes, containing old blood pigment, numerous dilated vessels and cystic areas. This tissue was merging with a neoplastic growth located in the occipital lobe, consisting of densely packed immature glia cells and glial giant cells.

An especially interesting and important case was reported by Merzbacher and concerns a young man, who developed immediately after a fall on his head the symptoms of a skull fracture affecting the right side. Some time after the accident epileptiform attacks occurred with increasing severity and frequency. At his death, which ensued three and a half years after the injury, two large tumors were found in the right brain at autopsy. The two tumors differed in color and consistency and one partly surrounded the other. The more superficially located neoplasm originated from the pia-arachnoidea, while the second blastoma was situated beneath, originating from the cerebral tissue. The demarcation between the two tumors was sharp in places, while there was a mutual penetration in other areas. In addition to the blastomas several foci of traumatic softening surrounded by a zone of glial tissue were found in the brain. The histological examination of the tumors showed that the meningeal neoplasm was a sarcoma, while the cerebral lesion was a glioma.

This unique case of a traumatic double malignancy of the brain of histogenetically different neoplasms forms a counterpart to a case reported by Nippe in which two blastomas, a glioma and a lipoma, were found at autopsy in the brain of a man who had sustained a cranial injury some time before. Since in the history of this case the pre-accidental, but transient occurrence of epileptiform attacks was noted, the conclusion was drawn that the lipoma had been present in the brain before the trauma. Marburg as well as Dürck mention the occurrence of allegedly traumatic gliomas of the spinal cord, but such claims are relatively rarely made in comparison to those advanced concerning the traumatic origin of cerebral gliomas.

B. Meningeal Neoplasms

The arachnoid-pia exhibits a predisposition to an excessive overgrowth after traumatic injury associated with hemorrhage. The resulting cellular proliferation has the macroscopical and microscopical appearance of a sarcomatous growth (pseudosarcoma).

The case reported by Merzbacher provided an example for the traumatic causation of malignant tumors of the meninges. Meningeal neoplasms of traumatic genesis are, as a rule, not malignant but benign in character. The dural meningiomas are well circumscribed, slowly growing proliferations of arachnoid cells of oval or elongated shape, arranged in bundles. Morphologically they occur in two forms, the so-called endotheliomas or angio-endotheliomas and the psammomas. Growing by expansion they may cause a local compression of the brain at the site of a former cranial injury (von Monakow; and Richter). This effect is responsible for the appearance of symptoms of general intracranial pressure following those of focal nature from the site of the tumor. Through pressure upon and erosion of the bone above the meningeal growth a hyperostotic reaction may be elicited, which must be distinguished from any periosteal osteomatous response caused by the trauma directly. The experimental production of malignant meningiomas in guinea pigs was reported by Daels and Biltris. The tumors appeared 15 to 30 months after the implantation of a glass seed containing radium bromide into the meningeal space.

C. Tumors of the Peripheral Nerves

Mention may be made finally of certain blastomatous and blastomatoid formations observed in the peripheral nerves and of their relation to trauma. A neurinoma of traumatic origin due to an activation of a preformed anlage was reported by Vogeler. While it may be possible that a local traumatic insult to a peripheral nerve may determine occasionally the localization of such a tumor, it is entirely improbable that such an episode has any effect upon the causation of this neoplastic disorder of the peripheral nerves. Ample and reliable evidence exists pointing clearly and unmistakably to the importance

of congenital factors in the production of this systemic disease of the peripheral nerves (neurofibromatosis).

Trauma plays a doubtful role in the causation of neurogenic sarcomas, according to Cutler and Quick, who obtained a traumatic history in 19.3 per cent of their cases (14 out of 72). Hartman stated that trauma cannot be considered as a true etiological factor in the production of these tumors, although it may be an activating one, while Coley and Higinbotham asserted that neurogenic sarcomas may have a traumatic origin.

Neuromas, which are blastomatoid hyperplasias of Schwann's cells, fibroblasts, and nerve fibrils, are the result of traumatic injuries to peripheral nerves (Faworsky). While they are observed most frequently as so-called amputation-neuromas in the stumps of amputated extremities, they are seen occasionally as painful, nodular formations in nerves previously exposed to some kind of trauma.

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X

OCCUPATIONAL TUMORS OF THE ENDOCRINE GLANDS

NO DATA are available concerning the occurrence of occupational tumors of the endocrine glands (hypophysis, thyroid, parathyroid, thymus, island apparatus of the pancreas, and suprarenal), excluding the gonads of both sexes, since they are considered in connection with the occupational neoplasms of the internal genital organs. There exist only a few studies on the experimental production of blastomas in the endocrine organs by the application of exogenous agents possessing an occupational significance. In view of the fact that these investigations may furnish some clue as to the possible causation of endocrine neoplasms in man, they are presented here with the hope that these studies may serve as a stimulus to more extensive work in this important field in the future.

The intracerebral injection of benzpyrene dissolved in oil into the brains of rats was followed by pituitary adenomas in 3 out of 10 animals (Oberling, Guérin, and Guérin). While these results could not be confirmed by Weil, when he injected dibenzanthracene or methylcholanthrene into the brain of rats, this investigator obtained similar adenomatous responses of the hypophysis, when styryl 430 was employed. It is doubtful whether any direct causal connection exists between the chemicals applied and the tumors observed.

The influence of extraneous factors upon the local incidence of blastomatoid and blastomatous conditions of the thyroid is a well-established fact. The nutritional deficiency of iodine in the regions with endemic goiter is related to the causation of functional and morphologic proliferative changes of the thyroid, and the possession of a goiter predisposes this organ to a malignant disease. Carcinoma of the thyroid is thus 20 times more frequent in Switzerland, where goiter is endemic, than in certain goiter free regions of the United States. Similar relations have been noted to exist in the goiter regions of the United States among human beings as well as dogs (Davis). Identical conditions prevail in regard to thyroid adenomas (Wagner-Jauregg; and McClendon). While benign adenomatous nodes are frequently found in thyroids, these neoplasms are much more frequent and reach much larger size in regions with endemic goiter. In non-endemic goiter districts these circumscribed hyperplasias remain in general so small, that they do not affect the shape and size of the thyroid. In regions with endemic goiter from 2.5 to 4 per cent of all cancers are found in the thyroid, while in non-goiter areas the relative

frequency of thyroid malignancy is only from 0.4 to 0.5 per cent. Recent experiments with a coal tar dye, ortho-amino-azotoluene, have yielded metaplastic squamous cellular lesions in the thyroid of guinea pigs, which had received this chemical with their food (Yoshida). The occurrence of these squamous-cell proliferations in the follicles in association with simultaneous follicular disintegration and fibroblastic proliferation is of significance in connection with cancerigenesis, as such metaplastic foci are considered by many investigators as embryonic cellular displacements possessing neoplastic potentialities and giving rise to the relatively rare squamous-cell carcinomas of the thyroid. Heep, who fed rats with ortho-amino-azotoluene, encountered in the thyroid of only one rat a duct lined with squamous epithelium, which he regarded as a residue of the branchial cleft and not as the result of an epithelial metaplasia brought about by the chemical introduced. The follicles of 40 per cent of the rats showed a solid proliferation of small epithelial cells. Among twenty-nine mice fed with ortho-amino-azotoluene, Brass noted two mice with squamous epithelial foci, but he was undecided whether these were metaplasias or congenital malformations. Severe hyperplastic changes, similar to those present in exophthalmic goiter in man (papillary hyperplasia of a columnar follicular epithelium and epithelial desquamation into a liquefied colloid), were obtained by Brass in guinea pigs which received arsenic and scarlet red oil with their food. Hellwig described metaplastic squamous epithelium in the thyroid adenoma of a rat which had been kept on a calcium rich diet. Twort and Ing found thyroid adenomas in mice painted with carcinogenic mineral oils.

These observations demonstrate that certain industrially important chemical agents may possibly produce, in persons exposed to them, hyperplastic changes of the thyroid and metaplastic precancerous lesions. In discussing the histogenesis of these squamous metaplasias in relation to thyroidal cancer, Jaffé pointed out that the squamous-cell islands of the thyroid, when found in the gland of a new-born infant or small child, may be of vestigeal, embryonic character. This explanation will meet with objections when it comes to account for the occurrence of squamous epithelium in thyroid glands which are the site of severe pathological changes, especially when present in adult individuals. In such circumstances the requirements are fulfilled for the causative mechanism of metaplastic changes, that is, old cells degenerate and young and not yet fully differentiated cells proliferate and meet with changed environmental conditions (Lubarsch). If the proliferation of the metaplastic squamous epithelium assumes the properties of an autochthonous growth, neoplasms will result, which, at first glance, suggest a dysontogenetic origin (Jaffé). It is difficult to conceive that nests of fetal cells should remain dormant over long periods of time before starting to proliferate. These observations and considerations suggest again the possible causal role exogenous agents of occupational origin may play in the production of tumors, which,

heretofore, have been attributed generally to an activation and malignant transformation of misplaced embryonic rests.

Nicotine, a parasiticide extensively used in recent years in agriculture and horticulture, has been incriminated in the development of adenomatoid hyperplasias in the medulla of suprarenal glands of rats (Staemmler). This investigator injected subcutaneously 0.1 mgm. of nicotine daily over a period of several months into rats, and observed at autopsy nodular formations of benign but occasionally infiltrative character in the suprarenal medulla in six of the twelve thus treated animals. The nodes consisted of indistinctly outlined acini composed of large, plasmatic cells, which contained light stained nuclei with a poor chromatic structure. The very vascular nodes were sometimes multiple. The chromaffinity of the cells was lower than that of the surrounding normal medullary cells. The cortex of the affected glands was atrophic. The development of these nodular hyperplasias is attributed by Staemmler to a stimulating action of nicotine upon the function of the medulla. This observation is important as it may suggest the presence of causal relations between exogenous agents, hormonal disturbances, and neoplastic growth.

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[XI]

OCCUPATIONAL AND ACCIDENTAL TUMORS OF THE SEX ORGANS

1. OCCUPATIONAL AND ACCIDENTAL TUMORS OF THE MALE SEX ORGANS

THERE exists great uncertainty regarding the presence of causal interrelations between occupational activities and cancers of the internal male sex organs (testis, epididymis, spermatic cord, prostate, and seminal vesicle).

A. Prostate

In a statistical study of the incidence of cancer of the prostate in certain occupations, Henry, Kennaway, and Kennaway found that of 46 occupations investigated the following had ratios above 150 (general population taken as 100): Patent fuel workers, 250; cellarmen, 200; gas works managers, 333; gas fitters, 210; brick kilns and oven men, 222; and gas stokers, 229. While this list suggests that individuals exposed to tar and tarry products show an increased susceptibility to prostatic malignancy, there is a striking exception to this apparent rule presented by the low incidence of cancer of the prostate in workers employed in tar distilleries (ratio 83). Henry and his associates were not convinced that these occupations are consistently predisposed to prostatic neoplasia, while exhibiting such relations in regard to the urinary bladder.

Apart from this doubtful circumstantial evidence favoring an exogenous causation of prostatic malignancy in man, there exist a few experimental observations which support such a possibility. Many years ago Bullock and Rohdenburg reported that the injection of scarlet red into the prostate and seminal vesicles of rabbits was followed by atypical and metaplastic epithelial proliferations. Experiments with carcinogenic polycyclic hydrocarbons, performed in recent years, showed that these compounds are capable of producing prostatic cancers (Cook).

B. Testis

a. Experimental Testicular Tumors

1. CHEMICAL AGENTS

Testicular tumor formation on an occupational basis is unknown, and data on the experimental production of cancers of the testis are scanty. The injection of tar into the testes of five rabbits, practised by Lacassagne and Monod, was followed in only one instance by the development of a sarcoma, appearing 355 days after the introduction of the tar. The direct injection of 1.2.5.6-

dibenzanthracene into the testes of rabbits resulted in the production of a tumor, probably derived from adrenal rests which occur normally in the rabbit testes (Lacassagne). The insertion of pellets of cholesterol containing 5 per cent of 1.2.5.6-dibenzanthracene or 1:2-benzpyrene into the testicle of mice gave a negative result in the hands of Ilfeld. A similar outcome was reported by Woglom, who placed threads soaked in 1:2-benzpyrene into the testes of rats and mice, as well as by Rusch, Baumann, and Maison, who injected 1.2.5.6-dibenzanthracene into the testes of rats. Lacassagne and Monod produced testicular sarcoma in rabbits by the intratesticular injection of tar. Interstitial cell tumors were produced by the implantation of stilbestrol or by a massive treatment with estrogens of mice (Shimkin, Grady and Andervont; Bonser and Robson; Hooker, Gardner and Pfeiffer). Mention may be made of the production of teratomatous carcinomas and adenocarcinomas of the testes in roosters after the intratesticular injection of a 5 per cent solution of zinc chloride (Michailowsky). This investigator obtained 5 tumors in 3 animals among 214 testes injected in 62 birds. This procedure resulted only then in neoplastic developments, when the injection was made during the months of January to March, during a period of physiologically marked gonadal hypertrophy and proliferative activity. These observations were substantiated by Bagg, but could not be confirmed by Ljvraga, who obtained only granulomas following a primary production of testicular necroses. Additional doubt of the primary causal significance of zinc chloride in regard to cancerous, testicular manifestations was aroused by the report of Mashar, who frequently found intraabdominal teratomas in roosters.

Similar experiments were conducted recently by Anissimova; and Falni and Gromzewa, who could successfully produce benign teratomous nodes in the testes of a few of the fowls injected with zinc chloride or zinc sulfate solution, respectively. The attempts of Willis to duplicate these neoplastic reactions in rats were unsuccessful. This investigator injected in addition to zinc chloride the following agents: potassium permanganate, hydrogen peroxide, pyrogallol, alcohol, ether, silica, and blood. None of these chemicals elicited a tumorous response. It may be of interest in this connection to refer to the observation of Giaya, who found the greatest concentration of zinc under normal conditions in the central nervous system, the prostate, testicle, and thymus. Considerable quantities of zinc are present in the spermatic fluid (Bertrand and Vladesco).

The evidence available, while not permitting a definite decision as to the causative mechanism active in the production of testicular neoplasms following the injection of zinc chloride, indicates, nevertheless, that this compound is not directly carcinogenic. As it is a necrotizing agent, it may exert a nonspecific effect by accentuating or modifying a normal stimulating action of the gonadotropic hormone upon congenitally predisposed cell complexes in a state of regenerative, hyperplastic proliferation.

II. PHYSICAL AGENTS

Among the physical agents, radiating energy in the form of roentgen rays and rays from radioactive substances does not seem to display any cancerigenic effects on the male sex organs, in spite of the relatively frequent occurrence of testicular atrophy following an occupational or therapeutic exposure of the male gonads. While the actinic destruction of the spermatogenic epithelium by the rays may be accompanied by a marked proliferation of the Sertoli's cells in some cases, a neoplastic transformation of the hyperplastic regenerative response of these cells has never been observed. The implantation of mesothorium into the testes of seven rabbits did not cause any neoplastic developments (Uehlinger and Schürch). This observation demonstrates that actinic atrophy alone, probably even combined with cellular mutation, is not sufficient for the subsequent development of cancer.

b. Trauma

Mechanical trauma has been incriminated often as a causative factor in the production of testicular neoplasia [Oberndorfer (citing in addition to three personal cases, those reported by Hedinger; Eiselsberg; Laskowitz; Kopas; Ulrichs; Fansler; Wegelin; Dull and Kutzmann); Müller (R); Fischer-Wasels; Kelley and Hueper; Ophüls; Thorek; Dew; Illingworth; Coley; Collins; and Rea]. This conception is rejected for various reasons by a great number of other investigators (Ewing; Barkmeyer; Berblinger; Wasterlain; Lubarsch; and Knox).

Much of the argument concerning the possibility of a traumatic etiology of testicular neoplasms revolves around the controversial histogenetic character of these tumors. Some authors contend that the great majority of benign and malignant testicular blastomas are teratomatous in nature, and are derived from congenitally misplaced, embryonic, omnipotent sex cells which may proliferate and form a mixture of adult and embryonic tissues upon which a malignant process may be engrafted (Ewing; and Klossner). It is maintained by the supporters of this theory that a single acute trauma is incapable of setting in motion such a complex development, and that trauma is, therefore, merely a coincidental phenomenon. Attention is called by these investigators to the fact that horsemen do not suffer more often than the general population from testicular neoplasia, in spite of their greater opportunity for accidental testicular trauma.

The argument is advanced that the normal testis has a remarkable facility to escape injury from all except rapidly moving, hard objects, while the testis harboring a tumor is traumatized more easily. The presence of a tumor may be masked for a long time by a co-existing hydrocele and thus escape discovery, until an accident to this organ calls attention to a testicular mass. Additional support for this conception is believed to come from the observation that tumor formation in the traumatically less exposed ectopic testis

(inguinal canal or abdominal cavity) is approximately one hundred times more frequent than in the scrotal testis (De Bary).

A critical analysis of these arguments reveals the fact that some of them are factually insecure or permit a different interpretation. It is by no means generally recognized, for instance, that almost all malignant tumors of the testis are teratoid in nature (embryonic carcinoma, seminoma, adenocarcinoma, and chorio-epithelioma). While, doubtlessly, an appreciable number of testicular cancers show histologically structures indicating a teratoid origin, there have been observed a great number of seminomas, in which even a thorough and careful search did not yield any evidence of a teratoid component (Deitermann; and Kelley and Hueper). That there exists apparently a fundamental causal difference between teratoid testicular tumors and those of seminomatous character is indicated by the discrepancy observed in the age distribution of these two types of neoplasms. While the average age of the individual affected by a seminoma is 40 years, that of a person with a teratoid carcinoma is only 28 years (Gordon-Taylor and Till). Seminomas are unknown in young persons, while the embryonal carcinomas of allegedly tridermal origin are the testicular neoplasms seen in childhood (Campbell).

Regardless of the developmental origin of testicular cancers, it is scarcely conceivable that a single and acute trauma is capable of initiating a neoplastic response in a formerly normal and intact organ. This conception, on the other hand, does not eliminate the possibility or probability, that a mechanical trauma to the male gonad may act as a contributory cancerigenic factor by activating a predisposed focus or organ (misplaced embryonic cells and hormonal disturbances). Such a viewpoint is in perfect agreement with the Cohnheim theory of carcinogenesis.

Assuming it is correct that a normal testis is not easily injured, it becomes even more remarkable that the statement of an accidental trauma of a more or less severe nature appears so frequently in the history of these cases (Deitermann: 42 per cent; Dew: up to 50 per cent; Chevassu: 10 per cent; Rea: 38 per cent; Kober: 28 per cent; Coley: 33 per cent; and Gordon-Taylor and Till: 20 per cent). Ophüls has pointed out that the claim of a traumatic factor in the causation of testicular malignancy is supported by the fact that these tumors occur mainly in young men in the prime of life, when the testicular epithelium is active. This observation has a certain parallelism in the appearance of testicular tumors in roosters, after the injection of zinc chloride during the period of heightened physiologic testicular activity. In regard to the predisposition of ectopic testes to malignant changes, it may be pointed out that the testis located in the inguinal canal is more exposed to mechanical trauma than the scrotal testis, and that the abdominal testis is in general an eminently pathological organ. An observation made by Boyd in identical twins, the one affected with a testicular tumor at the age of 31, while the second developed it at an age of 26 after being hit by a board on the

subsequently diseased testis, suggests that the trauma only accelerated the tempo of the cancerization process to which the testis was predisposed congenitally.

The occurrence of malignancy in an abdominal testis following a traumatic injury to this organ deserves special attention. The development of a seminoma in a man, 35 years old, who had sustained 16 years previously a testicular injury resulting in the luxation of a scrotal testis into the abdominal cavity, was reported by Schürer-Waldheim. The possibility of a direct traumatic injury to a primary abdominal testis was illustrated by a case recorded by Merlin. This author noted in his case that a blow into the hypogastric region caused the luxation of a retroperitoneally located testis into the abdominal cavity, accompanied by a separation of this organ from its normal appendages and vascular connections. The accident was followed by the appearance of severe pain in the abdomen. There was a hemorrhagic ascites four weeks later. A fist-size seminoma with extensive intraabdominal metastases was diagnosed eight weeks after the accident. In view of the large size of the primary tumor and the widespread metastases found so soon after the accident, Merlin maintained that the neoplasm existed at the time of the accident and was not the result of it, but was activated in its development by the trauma.

These two citations illustrate rather strikingly the great uncertainty existing in adjudging the relations of the trauma to the time of the appearance of neoplastic symptoms and the extent of neoplastic involvements. In some instances of alleged traumatic testicular cancer the swelling of the testis after the accidental injury did not recede at all or only slightly, before a progressive neoplastic enlargement became manifest (Most). In other cases there was a complete recession of the traumatic effects for a prolonged period, extending from a few months to several years, before a cancerous growth in the testis was noted. In a comment upon this aspect Oberndorfer stated that general clinical experience has shown that after the inciting stimulus has acted the growth of the tumor may be slow in the beginning, so that the injured person may appear to be normal for an extended interval, but frequently a sudden rapid growth may follow such a period of slow proliferation (Loenhard).

There exist considerable differences in the average growth rate of different types of testicular cancers (embryonic carcinomas being the most rapidly growing ones). This factor must be given proper consideration in medico-legal decisions of cases of this type. It is advisable to remember that the great majority of testicular tumors have neither primary nor contributory etiological relations to a trauma, and that only a severe trauma to a neoplastic testis may be regarded as an aggravating factor. The severity of the particular trauma may be judged more reliably perhaps from the immediate symptomatic effects produced than by secondary anatomical manifestations. A testicular trauma elicits a peculiar "testicular" pain, which in severe trauma is progressive and may result in a shock persisting for a considerable period. In all instances in which a trauma causes a marked and persistent swelling and induration of

the testis, it may be advisable to perform the Aschheim-Zondek test, by which the presence of certain types of testicular tumors can be ascertained (Ferguson; and Dean).

2. OCCUPATIONAL AND ACCIDENTAL TUMORS OF THE FEMALE SEX ORGANS

A. General Etiological Aspects

No information exists concerning the occurrence of occupational tumors of the internal female sex organs (ovary, oviduct, uterus, and vagina). The location of these organs practically excludes a primary and direct effect of an occupational carcinogenic agent upon these tissues, with the exception of the action of penetrating radiating energy (roentgen-rays and radioactive substances). No case of an actinogenic cancer of the sex organs, resulting from an occupational exposure to agents of this type, has been placed on record so far. Theoretically there exists the possibility that some of these organs, especially the oviduct and uterus, may act as organs of excretion of carcinogenic agents (aromatic substances, such as dyes and tar, and parasites), which have entered the body through other systems, and may become the site of an occupational neoplasia.

While some evidence exists suggesting an excretory activity of the tubal and uterine mucosa in regard to aromatic compounds and although cancerigenic parasites (Schistosoma haematobium) (Hutchison) may involve these organs, the development of neoplasia in the female sex organs on such a basis is unknown. The present clinical and experimental information available indicates that apparently intrinsic factors (hormones) play an important rôle in initiating neoplastic responses in these organs (Gardner, Allen, Smith, and Strong; and Halter), while exogenous factors may be operative mainly as contributory or adjuvant agents. That mechanical and inflammatory-bacterial, chronic traumatization of the cervix does not represent a major and essential cause of cervical malignancy is demonstrated strikingly by the fact that cervical carcinoma is rare in completely prolapsed uteri, in which the cervix is exposed to continuous frictional trauma as well as to bacterial, chemical and inflammatory injury (Craver; and Högler) (cervical cancer is 6 times more frequent in non-prolapsed uteri than in prolapsed ones).

B. Experimental Tumors of the Female Sex Organs

The apparent absence of extraneous occupational agents in the causation of neoplasms of the female sex organs (Hauser) does not indicate that these tissues do not react to the known carcinogenic agents involved in the production of occupational cancer. Repeated intravaginal injections of tar into rats by Teutschlaender resulted in the production of cholesteatoma-like formations in the uterine horns. There was observed in one rat out of nine thus treated the development of a cancroid of the uterine portio. This experiment was repeated by Fels, using mice. After seven months of treatment this investigator obtained

carcinoma of the vulva in one mouse. The vaginal epithelium responded only with a transient and reversible colpokeratosis. Malignant neoplastic responses were obtained by several investigators by the introduction of tar directly into the uterine lumen of rats and mice. There occurred both squamous-cell carcinoma and adenocarcinomas, while mixed forms were seen exceptionally (Momigliano; Cioli; Badile and Maurizio; and Orrù). The introduction of scarlet red into the oviducts of chickens resulted in the development of adenocarcinomas in 3 out of 40 chickens thus treated (Yamagiwa and Ohuo)

More recent investigations indicate that the direct and systemic introduction of synthetic carcinogenic chemicals may elicit carcinogenic responses in the uterine mucosa of animals (mice and rats). An epidermoid carcinoma of the uterine endometrium was observed by Ilfeld, following the intrauterine introduction of pellets consisting of 1.2.5.6-dibenzanthracene and cholesterol. The appearance of papillomas of the uterus, vagina, and ovarian cysts, after the cutaneous application of 1.2.5.6-dibenzanthracene and theelin, was reported by Perry and Ginzton. Burrows obtained evidence that the incidence of uterine carcinoma in rabbits can be influenced by the introduction of some of the known carcinogenic chemicals, similar to the effect exerted by these compounds upon the frequency of pulmonary neoplasms. Commenting on this observation Cook, Haslewood, Hewett, Hieger, Kennaway and Mayneord expressed the opinion that this action may be due to a summation of the stimulus exerted by the carcinogenic exogenous agent with that coming from an unknown, naturally occurring carcinogenic factor.

These neoplastic manifestations, remote from the site of primary contact with a carcinogenic substance, are of great general importance as they suggest the possibility of a more general carcinogenic action of occupational, environmental and other exogenous agents upon the female sex organs. Such an effect may possibly be exerted by the application of certain compounds used for medicinal purposes (coal tar dyes and tar preparations) or contained in cosmetics (estrogenic substances contained in creams, nasal sprays, and vaginal suppositories) (Moore, Lamar, and Beck; and Meyer). The possibility of such reactions in female sex organs is suggested by the fact that extracts of bituminous coal have been shown to possess estrogenic action (Tang, Wang, and Peng).

Finally mention may be made of an observation of Furth and Furth; and Furth and Butterworth, who reported ovarian tumors in mice irradiated during youth with small doses (200-400 r) of roentgen-rays (granulosa cell tumors and luteomata).

C. Trauma

While abdominal trauma of an occupational nature has not been shown to be responsible in any significant role in the production of tumors of the female sex organs, a mechanical accidental injury to the abdominal wall may

very well cause an aggravation of a preexisting neoplasm in these organs. An abdominal trauma may thus produce a rupture of an ovarian cyst, resulting possibly in a serious aggravation of the natural course of such a neoplasia by causing a spreading of tumorous implants in the peritoneal cavity. Such an event not only hastens the progressive course of a malignant ovarian cyst, but also changes fundamentally to the worse the outcome of a benign papillary ovarian cystoma. A trauma to the pelvic region of the female abdomen may also elicit hemorrhages and necroses in preexisting uterine fibroids, and may produce at least temporarily an aggravation of the tumorous condition.

Hertzler claimed that occasionally a malignant transformation of a uterine fibromyoma into a leiomyosarcoma may ensue after an abdominal trauma. Such an event may cause a torsion of the pedicle of pedunculated tumors (ovarian or uterine) and produce an acute and severe aggravation in the neoplastic condition, resulting from the necrosis in the neoplasms caused by the interrupted blood supply.

D. Tumors of the Mammary Glands

The mammary glands develop during embryonic life in both sexes by a downward growth of anlagen in the skin, and are of ectodermal origin in contrast to the reproductive organs proper, which are of mesodermal derivation. While the mammary glands of the male remain in an inactive atrophic state under normal conditions, those of the female undergo, with the onset of sex hormonal activity during puberty, a progressive development which in later life undergoes rhythmic changes paralleling the menstrual periods. The hormonal control exerted by the reproductive organs proper upon the morphology and function of the female breast becomes particularly evident during and after pregnancies. In view of these intimate interrelations existing between the reproductive organs and the mammary glands, it was considered advisable to present the occupational and traumatic aspects of mammary cancer in connection with those of the female sex organs.

a. Occupational, Biological, and Experimental Aspects

The only evidence relating the causation of cancer of the mammary gland to an exposure to an occupational carcinogenic agent is a doubtful one, and is related to the observation of bilateral mammary malignancy in two female roentgenologists (Depenthal; and Vigdortschik). While neoplastic malignant lesions affecting the fingers preceded in the case reported by Depenthal the appearance of the carcinomas in both breasts, there always exists a degree of uncertainty in the acknowledgement of a causal relation between an exposure to roentgen-rays and the development of a malignant tumor beneath the skin, if this organ does not show any signs of an actinic injury.

In spite of these meager data concerning an occupational causation of mammary carcinoma, the mere facts, that the breast is one of the most frequent

sites of malignancy among women, that mammary cancer causes death in a majority of cases, and that a constantly growing number of female workers enter industrial occupations entailing exposures of unknown and undetermined relation to the biological status of the mammary glands, seem to be sufficient grounds for giving this matter some attention in the future from a medical, medico-legal, and public hygienic standpoint.

This suggestion appears to be appropriate as recent investigations of Bittner; and Strong have shown that the incidence and development of the spontaneous mammary carcinomas, occurring in female mice of pure inbred strains and perhaps partially conditioned by a genetic, inherited, and hormonal factor, can be influenced to a high degree by various exogenous factors acting upon these animals at various stages of their postembryonic evolution. Bittner showed that the incidence of these so-called spontaneous mammary cancers was markedly reduced among the female offspring of mice of high cancer strains, when the litter were foster nursed by mothers of cancer resistant strains. The incidence of mammary malignancy was increased among the offspring of mice from a cancer resistant strain, when the litter was foster nursed by a mother from a high cancer strain. It becomes evident that in addition to the genetic factor determining any future carcinogenesis, there exists an additional and important extrachromosomal and environmental factor contained in the milk, and termed for this reason "milk factor," which exerts a marked influence in this respect. Bittner demonstrated subsequently that the same effect upon the future cancer incidence of low breast cancer females could be obtained when they were grafted with splenic, thymic, or lactating mammary tissue of young high cancer stock females. Hagedoorn concluded from this evidence that the so-called hereditary factor in cancer of the breast can be counteracted in mice by a simple intervention during early life.

The observations on the influence of various types of diet upon the incidence of "spontaneous" mammary cancer of mice, made by Strong, are even more startling and important. This investigator reported that female mice of the CBA strain showed an incidence of spontaneous mammary cancer of 4.8 per cent when kept on a diet consisting of rolled oats; while the frequency of these tumors increased to 26.3 per cent when these animals received a diet of commercial fox-chow. These findings, if applicable to the human, should be of utmost significance, as the mammary glands not only excrete estrogenic hormones having carcinogenic potentialities, but a large number of endogenous (colostric antibodies) and exogenous (aromatic drugs and arsenicals) substances, displaying definite biological properties and entering the organism by various routes (Schneider and Szathmáry).

In addition to these obviously nonestrogenic factors contained in the diet, there exist among the derivatives of tar a number of substances which display carcinogenic as well as estrogenic activities when administered to mice. Recent experimental studies of Loeb; Lacassagne; Gardner; Cramer; Burrows; and

Bonser have shown that an estrogenic hormonal imbalance, such as produced by an early and prolonged administration of estrogenic hormones, produces not only excessive hyperplastic changes in the mammary glands of mice, but also precipitates in these organs a malignant development [production of an internal carcinogenic environment (Cramer)]. It is not known whether or not a prolonged environmental contact with the aforementioned or other non-hormonal, extraneous, estrogenic substances may elicit similar effects in women, especially as there does not exist any agreement upon the role which a specific endocrine dysfunction or a prolonged therapeutic administration of female sex hormones play in regard to the initiation and development of mammary cancer in women (Lewis and Geschickter; Bromeis; Martynova; and Taylor).

The marked geographical and racial differences in the frequency of cancer of the female breast are attributed at the present time mainly to the existing variations in fertility of women in the different countries, incidence of abortions, and nursing habits, that is, factors which are apt to influence appreciably the endogenous hormonal environment and functional activity of the mammary glands. The experimental evidence presented suggests that exogenous influences may play an important role in this respect.

Kennaway and Sampson obtained intraductal papillomas in rats by the injection of tar into the main mammillary ducts of the nipple. This showed that the epithelial lining of the ducts reacts, upon contact with an exogenous carcinogenic agent, with a type of proliferative response, which in man is frequently the precursor of a malignant condition [Deaver and McFarland; Herxheimer; Bloch; Sebening; Tietze (in 10 per cent); Bloodgood (in 50 per cent); Greenough and Simmons (in 50 per cent); and Elliot (in 25 per cent)].

b. Trauma

The genesis and onset of carcinoma of the mammary glands in men and women has been related in an appreciable percentage of cases to a traumatic injury of the breast sustained some time previously. The data concerning the frequency with which trauma figures in a causal role in connection with mammary carcinoma vary greatly with different investigators and countries, and depend to a large extent upon the critical attitude observed by the various investigators toward the reliability and value of the historical evidence.

A few citations may suffice to illustrate this point. A traumatic factor was present in mammary cancer in the following percentage of cases, according to the various authors: Hildebrand, 2.6 per cent; Ziegler, 23 per cent; Schultheiss, 12 per cent; Horner as well as Kusche, 5 to 8 per cent; McWilliams, 44.6 per cent; Coley, 34.1 per cent; Deelman, English statistics, 37 per cent, Dutch statistics, 23 per cent; and Luff, 8 per cent (Schultz-Brauns). Lane-Claypon compiled the following table from data collected from numerous sources for the different countries:

INCIDENCE OF TRAUMATIC MAMMARY CANCER IN VARIOUS COUNTRIES (LANE-CLAYPON)

Country	No. Authors	Total Cases	Cases of Trauma	Percentage
England	5	742	129	17.4
America	6	1133	190	16.8
Germany	15	3003	244	8.1
Austria	2	858	88	10.2
Switzerland	4	495	60	12.1
Czechoslovakia	2	583	50	10.3
Norway	2	176	15	8.5
Denmark	1	210	14	6.6
Italy	1	204	11	5.4
Hungary	1	108	11	10.2
Total	39	7510	822	10.9

The great majority of these allegedly traumatic mammary carcinomas listed were attributed to a single traumatic episode. There are only a few cases on record in which a chronic or repeated injury to the breast was incriminated in the production of the mammary malignancy. McGraw and Schrankel reported such a case, in which a bilateral mammary carcinoma developed in a woman, 41 years old, who since childhood had used crutches which pressed and rubbed against the breasts while walking.

The above figures on the traumatic incidence of mammary cancer refer principally to that of the female breast, as those of the male organ represent only a small fraction of the total number (1.4 to 2 per cent) (Yamamoto; Mülleder; and Schuchardt). Although the constitutional conditions favoring a malignant development of the functionally and structurally inactive male breast must be considered as much less favorable than those present in the constantly changing and labile female breast, it is of definite significance that the proportion of allegedly traumatic and occupational breast cancers in males is relatively high (Mülleder). Manger noted a traumatic cause in 25 out of 71 cases of cancer of this kind (35 per cent), while Yamamoto found a traumatic history in 61 out of 257 cancers in male breasts (23.7 per cent). Wainwright who analyzed 418 carcinomas of the mammary gland of males commented on the high incidence of a traumatic history in these cases, and mentioned that a prolonged occupational trauma, such as exerted by the pressure of tools upon the breast (carpenters and shoemakers) seemed to particularly favor such a development.

In addition to the traumatic history presented by a considerable percentage of cases of breast cancer supporting the claim that a traumatic factor is sometimes involved in the causation of these neoplasms, attention has been

called to the fact, that about 50 per cent of all carcinomas of this organ are located in its upper outer quadrant, that is, in that portion of the breast which is most exposed to traumatism. As no other plausible explanation has been advanced for this phenomenon, Schultz-Brauns concluded that the possibility of a traumatic factor acting in a contributory or eliciting role could not be entirely excluded.

In refutation of this conception the following arguments were offered: Since trauma appears to elicit more readily a sarcomatous than a carcinomatous growth, it is remarkable that sarcoma of the breast is a very rare condition (Ewing; Deelman; and Deaver and McFarland). This argument loses some of its value because sarcoma of the breast occurs more often in men, who are exposed more frequently to occupational trauma, than in women [sarcoma in males: 5 to 13 per cent of all mammary tumors; sarcoma in females: 2 to 3 per cent of all mammary neoplasms (Schultz-Brauns)]. It is argued, moreover, that the glandular elements of the female breast are well protected by a layer of fat tissue from 0.5 to 1.0 cm. thick against numerous minor traumas sustained by this organ in the usual course of life (Ewing). It is doubtlessly correct that the adipose tissue of the breast affords a certain protection to the glandular parts against minor injuries, but not against severe ones. The question may be raised, whether or not such a factor is of great importance in connection with a traumatic origin of a malignant growth in the breast, as it can scarcely be maintained, that the mechanical trauma acts directly upon the epithelial elements in this respect. If there exists a traumatic causation of mammary cancer, such an effect is certainly connected with the production of necroses and hemorrhages in the interstitial tissue, their reactive sequelae affecting the vital activities of the glandular epithelium and the possible cicatricial retention of secretion. It is conceivable that a traumatic rupture of the connective tissue coats of the ducts may exert a similar influence upon the epithelial cells lining this part of the gland, especially when pathological hyperplastic processes exist in the duct (ductal papilloma) at the time of the injury, by stimulating the epithelial cells to grow invasively into the surrounding connective tissue.

The opponents of a traumatic origin of breast cancers maintain that these neoplasms may arise from a number of preceding, chronic, pathological lesions, such as chronic cystic mastitis, fibrous atrophic mastitis, simple atrophy of fat tissue, scars of old abscesses, displaced islands of glandular tissue, atypical recurrent fibroadenoma, eczema of nipple, catarrhal inflammation of nipple and terminal ducts, and papilloma of ducts (Ewing; and Adair). Cheatle and Cutler suggested that mammary cancer may be caused by a local irritation of the epithelial elements by altered secretions, such as is probably present in the content of cystic glands, ducts, and retention cysts. Arguing on the basis of these conceptions, Ewing demanded that, as there is no definite evidence indicating that trauma may activate the before-mentioned "precancerous" con-

ditions of the breast to undergo a malignant transformation, the demonstration of a general glandular hypertrophy of endocrine nature, or of a retention of glandular secretion in ducts and glands in a breast with an alleged traumatic carcinoma should rule out such a claim.

Apart from the fact that it will be difficult to prove in many instances whether or not the precancerous condition existed at the time of the accident, there remains the possibility for some of them, that they may represent a sequela of it. Greenough and Simmons maintained that ductal papillomas may develop, if the trauma causes fibrosing and obliterating changes in the breast resulting in the retention of secretion. They claim that a malignant transformation of such proliferative reactions of the ductal epithelium is a frequent occurrence. In a fair evaluation of the situation, one should not lose sight of the fact that the atrophic and hyperplastic changes found in the mammary gland, as the result of a disturbed functional and anatomical involution after the menopause, are so common in certain age groups that their mere presence cannot represent a just reason for denying a traumatic origin of a mammary cancer.

There exists sufficient clinical and experimental evidence, including that obtained from tissue cultures, which strongly suggests that necroses and hemorrhages may exert a growth stimulating influence upon the contiguous, intact, cellular elements. Since the epithelial hyperplasias seen in chronic cystic mastitis may merge insensibly into benign papillomatous as well as carcinomatous conditions (Cheatle; Charteris; Kueckens; and Hintze), and as such transformations occur, also, in the male breast (Kueckens; Pribram; Fischer; Wolff; and Theile), there does not seem to be any doubt that traumatic influences of the cited character may cause a hastening of such events, while probably not determining them. This statement does not imply that this is an obligatory course of events, as even marked traumatic destructions of the mammary tissue, such as seen in traumatic fat necrosis, are not followed by cancerous changes in the glandular elements of the breast (Knox).

The experimental approaches to this problem have given contradictory results. Lubarsch attempted unsuccessfully to produce mammary carcinomas in rats by subjecting spontaneous adenofibromas of the breast present in these animals to a crushing injury, or by injecting homologous and heterologous blood into the breasts over periods of weeks or months without causing any changes in the rate of growth, in the morphology, and in the number of mitoses in the benign tumors (Knox).

Bagg showed that a high proportion of female mice in which the young were removed from the mother at birth or whose nipples were ligated causing a retention of mammary secretion developed breast cancers. Similarly, Fischer reported recently that carcinomas developed from pieces of autogenously grafted mammary tissue of pregnant mice within 16 to 100 days after the transplantation into other parts of the body. While this observation seems

to present a striking experimental demonstration of carcinogenesis from a traumatically displaced part of the mammary glands, this conclusion can be accepted only with a certain reservation, as it is necessary to consider in this connection the existence of a genetic predisposition to mammary cancer, so frequently met in mice.

Many claims of allegedly traumatic cancers of the breast can be dismissed readily by considering the factors of time, intensity, and location of trauma, and the average growth rate of tumor present. In recognizing a traumatic contributory factor in the genesis of a mammary carcinoma the injury sustained must be sufficiently strong to cause structural changes and hemorrhages in the breast evidenced by the appearance of pain, swelling, and discoloration in the allegedly traumatized part of the breast. The interval between the injury and the manifestation of the neoplasm as well as its size and extent noted at that occasion must be properly correlated with the average growth rate characteristic for the different types of mammary carcinoma. It is not conceivable that a scirrhus carcinoma grows so rapidly that it becomes manifest within a few weeks after the trauma. Adherence to the overlying skin usually does not take place for some months, except in very malignant cancers (Ewing). Generally metastatic lymph nodes in the axilla are not observed in breast cancers of lesser malignancy before the lapse of one year. However, exceptions to these observations are not uncommon. Very small primary tumors of the breast, which are scarcely detectable by physical examination, may produce extensive metastases. The time of actual onset of these neoplasms, before the explosive type of metastization occurs leading to their discovery, is difficult to gauge. While the critical considerations advanced by Ewing are doubtlessly of great value in passing upon traumatic claims, it must be realized that their significance is of circumstantial nature. That in rare cases a traumatic origin of breast cancer must be conceded or appears very probable is admitted even by Ewing as well as Schultz-Brauns.

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XII

SPECIAL ASPECTS OF OCCUPATIONAL TUMORS

ATTEMPTS have been made to establish certain general characteristics and attributes for occupational cancers (Carozzi; and Feil). It was pointed out by these investigators that 1. these neoplasms appear rarely unheralded, but are preceded almost always by constitutional changes (toxemia) or by precancerous lesions; 2. they most often affect the skin, less frequently internal organs (lung, bladder, and bones); 3. the majority of occupational cancers are epithelial tumors, while sarcomas are less frequent; 4. primary neoplastic multiplicity is relatively common and may be of concomitant or successive type; 5. they develop usually after a prolonged occupational exposure to certain agents, but appear often at an earlier age period than the corresponding tumors of unknown etiology; 6. several factors may be concerned in their causation, making it difficult to distinguish between a preliminary, irritative factor and a secondary, final, inciting factor of possibly endogenous nature; and to this list may be added, that 7. the overwhelming majority of industrial neoplasms is found in males. Although many professional cancers exhibit these attributes, they are not pathognomonic and therefore insufficient for differentiating between cancers of occupational and nonoccupational origin.

Certain aspects of neoplasia relating to age, life span, heredity, susceptibility of organs, individuals, races, species, sex, multiplicity, and cutaneous pigmentation are more clearly discernible in occupational tumors than they are in connection with the cryptogenetic type of cancerigenesis. While some reference has been made to most of these factors as part of the presentation of the individual occupational tumors, their general fundamental significance warrants a more comprehensive discussion.

1. AGE AND SPAN OF LIFE

It is an assertion frequently made that cancer is a disease of elderly individuals, representing a manifestation of biological retrogression and being similar in this respect to arteriosclerosis (Feyrter). Cellular senescence is thus considered to be a direct or at least contributory cause of malignant growth. The appearance of cancers before the senile period of life is regarded by the supporters of the senescence theory of cancerigenesis as the result of a local precocious pathological tissue senility occurring on the basis of a congenital constitutional predisposition (congenital cellular misplacements and malformations of embryonic cells) or being brought about artificially by the action

of some specific or nonspecific endogenous or exogenous factor (solar rays, roentgen-rays, tar, and arsenic) during the postfetal period of life (Nemenow; and Koelsch). The prevalence of the various organ cancers at different age periods is fitted into this conception by assuming that different tissues undergo senescent changes at different age periods (Burkard; Macklin; Little; Wells; and Polland).

Wells contended that "placental tumors occurring as they do in fetal tissues, may not be an exception to the rule that from one fifth to one tenth of the life cycle of an organism ordinarily is required to produce a malignant growth, since the placenta is an organ the entire life cycle of which terminates in senility in about six months." However, this relation is non-existent in regard to most of the other malignant neoplasms observed in early childhood. An approximate idea about the way such a hypothesis works out in regard to post-fetal neoplasms may be gained from a list of different organ cancers arranged according to the incidence maximum at certain age periods (Holtz): 0-4 years, testes, kidney, and suprarenal; 15-25 years, bones; 30-35 years, testes; 40-50 years, brain; 50-55 years, female sex organs; 60-65 years, skin, and abdominal organs; and 70 years and more, prostate. Everybody would develop a cancer in some organ, according to this dogma, if he lived long enough (Burkard; and Macklin).

The senescence theory of cancerigenesis forms the basis for the statistical calculation, through which the appreciable increase in the absolute incidence of malignant tumors observed during recent decades is related etiologically to the coincidental rise in proportion of older age groups in present-day population (Haubold; Burkard; Crawford-Dunlap; Peller; and Jung). While it is often conceded that simultaneous improvements in diagnostic methods and general medical care doubtlessly contributed to some degree to this increase, by leading to the discovery of a larger number of malignant tumors than was previously the case, statistical data indicate that cancer death rates standardized for age showed from 1911 to 1935 a large increase. Those related to cardiac diseases, chronic nephritis, and cerebral hemorrhage, all of which, like cancer, are diseases of the older age groups, did not (Dublin and Lotka).

There is a progressive rise in cancer mortality with the advancement of age (Dublin and Lotka; and Gover), in spite of the fact that cancer is not a disease of old age, but more of the late middle age, as 60 per cent of all deaths from cancer in women and 50 per cent of all cancer deaths in men occur from 30 to 60 years of age (Haubold; Dorn; and Wells). It is maintained that the biological cancer menace has grown in recent times in the same measure as the group of cancer-susceptible old people increased (Blumenberg).

Attempts have been made to obtain supporting evidence for the senescence theory by pointing to the differences in the latency period of experimental cancers in various species of animals, which are claimed to parallel the variations in their normal life spans (Passey; Wells; Findlay; and Wood). It

is argued that the normal life span, by controlling the rate of tissue senescence, determines the speed of the development of cancer, and that chemical and physical agents produce cancer in man and animals in the same tissues and in relatively the same time period expressed in fractions of the usual span of life (Cramer). Hence experimental cancer is said to appear quicker in mice than in rabbits, in rabbits than in dogs, and in dogs than in man, that is, the time necessary for the induction of a cancer increases with the length of life of the species (Passey; and Wood). The normal life span of a dog is estimated to be 16 to 22 years or one-fourth that of man (Editorial, *Lancet*), that of a rat is given as 3 years or one-eighth to one-tenth of that of man, while that of a mouse is noted to be 2 years, rarely 3, or one-tenth to one-twelfth that of man (Wood).

There exists a great deal of reliable and important evidence indicating that old age or tissue senescence and cancer are, in general, incidental and concomitant in their relationship rather than cause and effect, respectively (Pack and LeFevre). Wells commented on the fact that a group of tumors that usually appear early in life or not at all did not seem to adhere to the general principle of tissue senescence and life span. This investigator concluded that presumably these relatively rare congenital malignant tumors, which appear chiefly before or soon after birth (retinoblastoma of the eye, neuroblastoma of the suprarenal, adenosarcoma of the kidney, extrasuprarenal neuroblastoma, and congenital sarcomas of various types), depend on some other mechanism or principle than do the ordinary malignant growths that require so long for their production. Cramer and also Wells suggested that this factor might be represented by the normal metabolic activity of the tissues susceptible to congenital neoplasia. These investigators pointed out that placenta, retina, brain, and renal medulla have normally a high glycolytic activity resembling that of the embryonic and cancerous tissues, and this may have some connection with the occurrence of these tumors in the early years of life.

These metabolic arguments are fundamentally weak, as the theory of Warburg to which they refer is largely discredited by now. The anaerobic glycolytic metabolism has been found to be not characteristic of tumor cells, but common to all injured cells (Druckrey) and dying neoplastic cells possessing an anoxybiotic glycolysis (Bierich), while vitally intact tumor cells exhibit approximately the same metabolic activity as the corresponding normal cells from which they are derived (Holtz; and Berenblum).

Wells noted that none of the congenital tumors observed in fetuses born dead and other congenital neoplasms were carcinomas commonly seen in adults, while some of the congenital sarcomas did not seem to differ from types found during more advanced ages. As the experimental production of sarcoma and carcinoma requires the same time, the reason for this discrepancy was not clear to Wells. The observed differences between sarcomas and carci-

nomas as to age become even more pronounced, if the normal age distribution of the two types of cancers is considered. The incidence of sarcomas of various types varies only slightly from age 20 to age 80, when one takes into account the number of persons actually living at different ages (Craver; and Pack and LeFevre), while only from 1 to 3 per cent of the carcinomas are found before the age of 30 years (Fowler; Körbler; Rosser and Kerr; Hall and Bagby; Weisensee; Helmholz; and Bruckner). Sarcomas represent 97 per cent of all malignant neoplasms in children, and carcinomas compose 90 per cent of all cancers occurring in adults.

It is scarcely ever maintained that cancers consist of cellular elements having the characteristics of old cells. On the contrary, cancer cells are considered often as cells which have preserved the qualities of very young, embryonic cells, expending their whole energy upon reproduction of their kind (Boyd). This conception is scarcely tenable in view of the abundant evidence that malignant neoplasms may display an impressive degree of differentiation, functional activity, and even organization. It is known from studies on normal cells in vitro that the degree of differentiation is mainly a coefficient of the proliferative activity.

This relation is apparently not always adhered to by malignant tumors. Basal cell cancers of the skin, for instance, usually grow slowly and never produce metastases, in spite of the fact that they are composed of morphologically immature cells, while some adenomas of the thyroid as well as certain fibromas of the stomach, although they display a high degree of cellular and structural differentiation, may give rise to extensive metastatic deposits.

Cramer pointed out, in connection with the alleged relation existing between life span, tissue senility, and carcinogenic latency period, that the aging process does not represent a determining factor in the development of malignant growths, as cancer can be produced as readily in a young organism as in an aged one. The reason for the characteristic age incidence of malignant tumors is to be found, in the opinion of this investigator, in the long preparatory period necessary for cancer induction. It is doubtful whether or not species specific differences in life span are directly reflected in the length of the carcinogenic latency period of the various species. The shortest latency period of experimental tar cancer is 50 days for mice, 47 days for rabbits, and 400 days for rats, while the longest recorded preparatory periods of this neoplasm is 540 days for mice, 560 days for rabbits, and more than 500 days for rats, whereas the guinea pig is entirely refractory. The latency period of experimental osteogenic sarcoma caused by radioactive substances is 11 to 35 months for rabbits, 5 to 30 months for guinea pigs, and upward to 60 months in human cases on an occupational basis. Uehlinger listed the following maturation times for malignant growths caused in various species by the action of radioactive energy:

Species	Radium	Thorium	Mesothorium	Time in Months
Mice	6.5–21	9–14		
Rats	7.0–22	10–27		
Guinea Pigs	8.0–30			
Rabbits	10.5–39		11–44	
Roosters	13.0–27			

This table shows that the latency period of radioactive malignancies is approximately the same not only for the different types of rays, but is also not appreciably at variance in regard to the different species in which the cancers were produced.

Evans and Goodman noted that rats and mice are about 40 times as resistant as humans to neoplastic lesions caused by alpha-rays, when all dosages are expressed in erg units. Thus, there exist great species specific differences in susceptibility, which have no relation to the normal life expectancy.

Observations made in connection with the experimental production of cancers in different species by the introduction of several synthetic chemical carcinogens (3:4-benzpyrene and 1.2.5.6-dibenzanthracene) prompted Shear to state, that the differences in latency period observed appeared to be accounted for satisfactorily by the variations in normal life span between the species tested. Barry and Cook reported that the length of time required for the production of tumors in rats and mice by the subcutaneous injection of 5.6-cyclopenteno-1.2-benzanthracene and 1.2.5.6-dibenzanthracene showed no relation to the difference in the respective natural duration of life of the two species.

Des Ligneris considered the following two possibilities as controlling the relations between lag period and life span of different species: 1. cancerigenesis may depend upon the fact that cells have to undergo a certain number of mitotic divisions before becoming malignant, and that division rate differs in various species; 2. or cells must metabolize and divide during a certain minimal part of the life span to become malignant, even under the most favorable conditions. Des Ligneris was uncertain whether any such relations existed at all.

It is a well-established fact that the length of the latency period of experimental as well as of the so-called spontaneous cancers in animals can be influenced by exogenous factors. The intensity and frequency of exposure to a particular carcinogenic agent controls to a certain degree this important factor in carcinogenesis (Hieger; Fieser, Fieser, Hershberg, Newman, Seligman, and Shear; and Rusch and Baumann). Rusch and Baumann noted that the latency period of ultraviolet ray cancer in mice was 3.5 months, if the daily period of exposure was 60 minutes, while it was increased to 9 months when the

exposure period was reduced to 10 minutes. Rabbits so far have proved refractory to the carcinogenic action of ultraviolet rays.

Fieser and his coworkers noted that marked differences exist as to the rapidity and regularity with which certain synthetic carcinogenic hydrocarbons induce tumors. These investigators determined the relative carcinogenic potency of a particular compound by the "average time", that is, the time required in 50 per cent of the animals (mice) tested to develop tumors. They found this time to be 2.5 months for methylcholanthrene, 3.5 months for 3.4-benzpyrene, and 7 months for 1.2.5.6-dibenzanthracene under certain standardized conditions. Variations in these figures could be produced by instituting changes in the technique of administration, in the type of solvent or vehicle, and the species and strain of animals used.

Experiences reported by Japanese workers on the hepato-carcinogenic action of certain azo-compounds and by American workers (Strong) with spontaneous mammary cancers in mice demonstrated clearly the influence of dietary factors upon the incidence and latency period of certain liver and mammary carcinomas.

In analyzing the factors which may influence the length of the latency period of experimental cancers in comparison to the occupational cancers, one should not lose sight of the fact that certain anatomical differences and metabolic variations [sometimes of dietary nature (herbivorous, carnivorous, and omnivorous habits)] may exert not only a deciding influence upon the preparatory period, but also on the susceptibility of different species to certain carcinogenic agents. There exists, for instance, a fundamental difference in the structure of the skin of mice, rats, rabbits, and man, involving the epidermis and appendiceal organs (hairs and sebaceous glands).

Hueper found in his recent experiments on the production of cutaneous malignancy in congenitally hairless rats and their haired litter mates, that the hairless rats with a shorter average life span (360 days) were less susceptible to the carcinogenic action of the ultraviolet rays than the normal haired rats, having an average life span of 555 days. The difference in reactivity in this instance was caused by the normally thicker and more keratinized epidermis present in the hairless rats.

Kinosita stated that the higher resistance of rabbits and guinea pigs to the hepato-carcinogenic action of butter-yellow was in part attributable to the fact that these animals excrete this compound quicker than rats do. This investigator mentioned that mice were less susceptible to butter-yellow than rats.

Comparisons between the latency periods observed in experimental animals and man often neglect the fact that the experimental conditions of exposure are usually very much more severe than those existing under ordinary occupational circumstances, and for this reason alone the latency period of occupational neoplasms must be longer in general than that seen with experimental cancers of the same genesis. The latency period of industrial aniline cancer of

the bladder is thus more than ten years, being only exceptionally very much shorter, while the preparatory period of the experimental variety obtained in dogs is about two years for the majority of animals. This difference is caused in part by the much more intense exposure to beta-naphthylamine to which the dogs were subjected (receiving from one-tenth to one-fourth of the single lethal dose of this substance daily), than that found in well conducted dye operations. An important additional reason for the species specific differences in susceptibility to the various carcinogenic agents is represented by the fact that the mechanical defense mechanism, operative in the detoxication of the chemical carcinogens, differs with the chemical nature of these substances and to a certain extent with the species. Young, who reviewed the information available on the detoxication of carbocyclic compounds, mentioned in this connection that rats, for instance, detoxify benzoic acid with glycine, and bromobenzene with cystine and methionine, which is converted into a mercapturate. Boyland and Levi showed that rabbits and rats both excrete anthracene administered orally as 1.2-dihydroxy-1.2-dihydroanthracene, but rabbits form the d-compound while rats form the l-substance.

Although aromatic amino compounds usually undergo in the animal organism acetylation, there exist species specific differences in this respect. Dogs excrete o-, m-, and p- aminobenzoic acid unchanged; man eliminates only the o-compound unchanged. Similar differences occur in the metabolic detoxication of such substances by the dog and rabbit, the latter species using the acetylation process more generally than the dog. While the dog excretes beta-naphthylamine as 2-amino-1-naphthol, this product could not be isolated from the urine of rabbits with the methods used for the dog's urine (Wiley), suggesting that an important difference in the conjugation products formed by these two species exists. Herbivores (rabbits) oxidize acetanilid in the para-position forming p-amino-phenol, conjugated with sulfuric acid and glucuronic acid through splitting off of the acetyl group. This metabolite can be isolated from the alkaline ether fraction of the urine, while no metabolite is obtained from the acid urinary fraction. Carnivores do not form any p-aminophenol in the basic extract, but convert the acetanilid into o-oxycarbanil, which is paired with the sulfuric acids and glucuronic acid, and appears in the acid urinary fraction. The oxidation of the acetanilid takes place under these circumstances in the ortho-position without the elimination of the acetyl group. The first conversion product is the unstable o-oxyphenyl carbaminic acid, which changes spontaneously into o-oxycarbanil. Variations in regard to the site of detoxication of certain compounds are found between the different species. Although the liver is considered usually as the main organ in which carbocyclic compounds are detoxified, the kidney represents a second and sometimes important site of detoxication.

Thus, a great variety of chemical defense mechanism may come into action and result in the formation of a large number of metabolites, differing in com-

position, structure, or configuration. In view of the known importance of these factors in regard to the carcinogenic quality of a given compound (Fieser), it is readily conceivable that such species specific differences in detoxication of "carcinogenic" compounds may be of great significance in determining the degree of susceptibility, and length of the latency period of carcinogenesis for different species.

Recent studies on the metabolic conversion of 1.2.5.6-dibenzanthracene in different species brought out the fact that the metabolite of this compound in mice and rats (Dobriner, Rhoads, and Lavin) differs from that excreted by rabbits (Levi and Boyland). In commenting on this phenomenon Cason and Fieser pointed out that a carcinogen may undergo two independent metabolic reactions in the body proceeding by different mechanisms. The one responsible for tumor formation may be a chemical substitution at the reactive meso-centers of the molecule, while the other leading to detoxication may be a reaction of addition, involving a different part of the molecule. The addition may take the form of "perhydroxylation" with a subsequent change to the phenolic form, or a combination with the disulfide bond of cystine to give a 1.2 addition product followed by the loss of cysteine and acetylation, thus producing the mercapturic acid derivative of the hydrocarbon. The two mechanisms are regarded as being competitive by Cason and Fieser.

The importance of senile tissue changes for the development of cancer is strongly refuted by the mass of evidence available from experimental studies on this subject (Woglom; Yamagiwa; Fibiger; and Bang). Even though Dunning, Curtis, and Bullock, who injected 3.4-benzpyrene into rats, observed that the induction time in young rats was slightly longer than in old ones, Brunschwig and Tschetter noted no difference in the latency period of two groups of rats, one composed of animals three weeks old and the second of rats 12 months old, after the introduction of methylcholanthrene.

Strong, Smith, and Gardner found that tumors developed earlier in young mice than in old ones injected with 3.4.5.6-dibenzcarbazole, using two different strains in their experimentation. Similar results were reported by Shimkin, who conducted an extensive series of experiments with mice of different ages injected with methylcholanthrene. From the results of these studies, he concluded that the evidence obtained supported the conception that the younger the tissue the higher is its susceptibility toward a malignant transformation under the influence of tar or related chemical carcinogens.

The conception that tissue senescence has no etiological relation to carcinogenesis receives additional and powerful support from observations made in connection with the age incidence of occupational cancers. Some conspicuous evidence to this effect is provided by the soot epitheliomas of the skin of chimney sweeps. During the days of Pott, Earle, and Curling (1780 to 1866) when chimney sweeps entered the profession as climbing boys at the age of 4 to 8

years, scrotal cancer became manifest during the ages of 30 to 40 years. Following the introduction and partial enforcement of laws restricting the employment of infants in this occupation, the manifestation age of the chimney sweeps' cancer increased to 45 to 50 years from 1872 to 1892 (Butlin), and advanced still further during the subsequent decades (1911 to 1935), when the average age of chimney sweeps with scrotal epithelioma was found to be 61.9 years (Henry). The manifestation of the majority of sweep's cancers was delayed by 25 years after the various governmental regulations controlling the employment of boys in this profession had been made more strict, the starting age of employment had been advanced to 16 years, and sanitary and technical improvements and medical measures had been introduced, reducing the intensity of exposure and combatting effectively the precancerous lesions. While Earle and Pott observed scrotal cancer in climbing boys as young as 8 years old, and whereas these tumors were not infrequent in sweeps from 15 to 30 years of age at that time, soot cancer is nowadays not seen before the age of 30 years and is rarely found in individuals between 30 to 45 years old.

Similar observations were made in England in connection with the manifestation age of paraffin and oil cancers. From 1911 to 1935 the manifestation age of this type of occupational tumor advanced by 12 years (1911-1915: 54.2 years average; and 1931-1935: 63.5 years average). Somerford attributed this development to the fact that the entrance age of the workers was formerly much lower, as it was a common custom to send children 9 to 10 years old into the factories.

Fibiger; Parodi; Döderlein; Leroux and Peyre; Bang; and Leitch emphasized the point that tissue senscence plays no role in the development of tar and pitch cancer. Pitch cancer is found in individuals between 19 to 79 years old, and tar cancer is observed among workers from 30 to 85 years of age. In a series of 362 tar cancers, 140 cases involved individuals less than 50 years old. Sladden showed that the incidence of pitch cancer among workers of patent fuel plants increased directly with the duration of employment paralleling the age of the workers, so that ultimately in the oldest group 100 per cent of the workers were affected by pitch epitheliomas.

While the age distribution of occupational arsenic cancer does not reveal any remarkable shift into younger age groups, such a phenomenon is prominently displayed by the non-occupational type of arsenic cancer (range: 10 to 80 years). Twenty-four out of 39 therapeutic arsenic cancers were in individuals less than 40 years old. Pye-Smith stated that 25 per cent of all therapeutic arsenic cancers affect individuals less than 35 years of age, while Ullmann found that this type of malignancy was usually seen before the age of 40 years.

Occupational cancer of the bladder of chemical or parasitic genesis is characterized by an age incidence which favors the younger age groups (aniline cancer: 52.4 per cent of all cases in individuals less than 50 years old; and

schistosomiasis cancer: in individuals 30 to 40 years old). Cryptogenetic cancer of the urinary bladder affects persons more than 50 years old (in about 75 per cent of the cases).

Roentgen-cancer of the skin is another occupational malignancy which frequently involves persons of early middle age (Hesse: 28 to 56 years, average 41.66 years; Hunter: 35 to 50 years; Saunders and Montgomery: 27 to 67 years, average 49.5 years for occupational cancers; and Holthusen and Englmann; 10 to 70 years for therapeutic cancers). A remarkable shift in the age distribution of lung cancer has been noted during the past 60 years in the Schneeberg district, paralleling to some degree the changes which were introduced in the working conditions in these mines. While the average age of the miners dying from pulmonary malignancy, caused evidently by the respiratory contact with radioactive matter, was in 1876 between 40 to 50 years (72.22 per cent died before the age of 50 years), the average age has advanced in recent years to 55 years (range 37 to 69 years). A still more pronounced disregard of the theory of tissue senescence was exhibited by the osteogenic sarcomas observed in luminous dial workers, who were from 20 to 30 years old when they died from their occupational malignancy, entering the hazardous work usually at the age of 18 to 23 years.

The evidence presented supplies convincing proof that the occurrence of cancer during the more advanced periods of life is mainly fortuitous and unrelated to any simultaneously existing senile tissue changes. Cancer appears to be an exposition disease of long duration requiring, in the average individual and under ordinary conditions of exposure to some known or unknown, exogenous or endogenous, carcinogenic agent, a considerable number of years before it becomes manifest. The appearance of cancers at an early age merely indicates that the affected individuals are particularly reactive to some kind of carcinogenic agent, the agent is extraordinarily potent, or the exposure started at an inordinately early period of life. The manifestation age of cancer thus depends upon various factors, such as, age at onset of exposure, intensity and duration of exposure, potency of the carcinogenic agent, and individual susceptibility (Hieger; Seelig and Cooper; Bang; and Deelman). Additional factors of endogenous or exogenous and specific or nonspecific nature are doubtlessly able to accentuate and shorten the developmental precancerous phase (solar rays, photodynamic substances, arsenic, and mechanical and thermic trauma).

2. SEX

The great majority of occupational tumors involves male workers. This condition is attributable to the fact that many more men than women are employed in operations entailing a carcinogenic hazard. While the incidence of industrial or professional malignancy in women is very low, according to the data available, there can be no doubt that this recorded information does

not reflect correctly the full extent to which female workers are affected by occupational cancers. Various reasons are responsible for this situation. The large scale employment of women in industry is of relatively recent date, and is to a higher extent of a transitory nature than is the case with male workers. The number of women exposed sufficiently long to some industrial carcinogenic agent is, therefore, not as large as that of men. The establishment of etiological relations between any carcinogenic occupational exposure sustained by women workers is interfered with to a noteworthy degree by the fact that many women leave the industrial employment, after several years, to become married and do housework. The occupational genesis of any cancer appearing many years after the cessation of exposure is much less obvious in women than in men and often missed. Female labor has been organized less extensively and effectively than male labor, and has benefited to a smaller degree by measures introduced by law for the improvement of working conditions and for the elimination of health hazards.

No evidence exists suggesting that sex conditioned factors influence appreciably the susceptibility of male and female workers to the various occupational agents causing neoplasia, unless these factors are related to differences in the type and degree of exposure to which the two sexes are subjected to an unequal degree, because of variations in the type of clothing, personal hygiene, diet, and use of cosmetics.

The occurrence of occupational cancers in female workers was recorded for the following types of exposures:

a. Physical Agents: Solar as well as roentgen-rays have given rise to cutaneous malignancy in female workers (Roffo; and Hesse). The occupational contact with radioactive substances has been responsible for the occurrence of osteogenic sarcomas and pulmonary carcinomas in women employed in luminous dial factories and radium laboratories, respectively.

b. Chemical Agents;

Arsenic: While occupational arsenic cancer of the skin has been observed in males only, therapeutic arsenic cancer has been seen repeatedly in females (ratio males to females = 4:1).

Tar and Pitch cancers have been seen in men only, but experimental tar cancer was produced with equal ease in male and female animals.

Oil and Paraffin epithelioma has been noted recently in female workers (Somerford; Henry; and Southam).

Soot: While the great majority of soot epitheliomas involves men, there are a few soot cancers in women on record.

Aromatic Amine Cancers of the bladder in dye workers are known to occur only in males, but have been reproduced experimentally in female dogs.

c. Parasites: Schistosomiasis cancer of the bladder in Egyptian fellahs attacks women rarely (male to female ratio is 50:2).

No equivalent occurs in women of the occupational scrotal cancer found in

men in connection with the exposure to soot, pitch, tar, paraffin, mineral oil, and arsenic. Anatomical differences between the scrotal and vulvar skin, higher personal cleanliness of the vulvar region, and absence of friction and direct contact with soiled clothing may be responsible to a large extent for this discrepancy.

3. RACE AND PIGMENTATION

The observation of marked differences in the incidence of cancers of certain organs in countries inhabited by different racial groups has raised the question whether etiological interrelations exist between genetically-conditioned racial factors and the relative susceptibility to neoplastic diseases in general and to cancers of certain organs in particular. Th problem has remained controversial, as a definite decision is made difficult by the fact that reliable statistical data regarding this subject are not available. Also, differences in the nature and extent of various environmental factors (diet, habits, and climate) cannot be properly appreciated as to the role they might play in bringing about such regionary fluctuations (Fischer; Sitsen; Auler; Rössle; and Hueper). There can be no doubt that various races and racial mixtures differ from each other not only in skin color and general build, but also in many more minute anatomical details, such as, the size of the heart, liver and spleen (Krumbhaar and Lippincott; Moon; and Rössle), the secretion of the apocrine and sebaceous glands, the type and color of hairs, the number and distribution of sweat glands, and the distribution of blood groups (Flössner) Thus, it is still uncertain, whether the unusual frequency of a limited number of diseases occurring predominantly, although not exclusively, in certain races is attributable to a racial factor, or represents merely an expression of an extraordinary crowding of special constitutional weaknesses or sensitivities in such racial groups propagated or accentuated perhaps by limited inbreeding.

In view of the great practical and scientific importance of this question it seems to be advisable to point out a number of diseases, which exhibit such racial bindings, before the neoplastic aspect is taken up.

Racial connections appear to be particularly prominent in several dyscrasias of the blood. Sickle-cell anemia occurs mainly in Negroes, who display in a certain percentage of clinically normal individuals a sickle-cell trait (Brandau; Anderson and Ware; Sydenstricker; Jeter; and Huck). In exceptional cases this disease has been observed in members of other races [Arab (Archibald); Cuban (Stewart); Italian (Castana); Greek (Cooley and Lee); Scottish-Irish (Sights and Simon); and white Americans (Haden and Evans)]. Cooley's anemia (thalassemia, Mediterranean disease) is found almost exclusively in members of the races inhabiting the eastern Mediterranean basin (Italian, Greek, Armenian, and Syrian) (Caminopetros; Whipple and Bradford; Jehndorff; Strong; and Wintrobe, Matthews, Pollack, and Dobyns). Hemophilia occurs most often among members of certain families belonging

to the white race, particularly its Teutonic branch and the Jewish racial mixture. It is only lately that this congenital and hereditary disorder of the blood has been seen in other races [Negroes and Japanese (Pachman; Crandall; and v. Verschuer)].

Recent studies on the racial incidence of pernicious anemia brought out the fact that the occurrence of this disease is not restricted to the white race, but is found, although less frequently, among members of other races (Friedlander; and Kampmeier and Cameron). Investigations of Dubois, Reznikoff, Foot, and Bethea revealed that polycythemia vera is much more frequent among members of the Jewish racial mixture than in the white race in general. Kracke and Parker contended recently that agranulocytosis is rarely encountered in the Negro and yellow races and is practically confined to Caucasians. Although agranulocytosis exhibits a preference for certain occupational groups (medical and nursing profession) especially exposed to an excessive use of analgesics and hypnotics, these apparent racial differences in the susceptibility to agranulocytosis merely reflect variations in the frequency and intensity of exposure to certain causally important drugs.

Among diseases of a noninfectious origin displaying a prominent racial relation, diabetes mellitus and pentosuria are outstanding examples. These two diseases show an excessive incidence and a high hereditary tendency among members of the Jewish racial mixture (Rudy and Keeler; Strauss; Lichtwitz; Priesel and Wagol; and Rolleston). Noguchi's disease, or familial night blindness, is observed exclusively among Japanese.

Similar conditions are encountered in connection with certain precancerous, blastomatoid and blastomatous diseases of nonoccupational origin. Several degenerative lipoidoses (idiopathic amaurotic idiocy, Niemann-Pick's disease and to a lesser degree, Gaucher's disease and xanthomatosis) are found much more often among members of the Jewish racial mixture than other racial stocks. The idiopathic hemorrhagic sarcoma (Kaposi), a blastomatoid disease of the vasculo-connective tissue, is observed most often in Italians (40 per cent of total number of cases), less frequently in Russians and Jews (20 per cent each), and Poles (about 8 per cent) (Pack; and Schubert). Xeroderma pigmentosum, a hereditary hypersensivity of the skin to solar rays leading ultimately to the development of cutaneous malignancy, seems to attack members of Jewish stock more frequently than other white races (Schubert), a fact possibly related in part to a more frequent occurrence of consanguinous marriages among Jews, which are blamed, also, for the occurrence of this disease among the Japanese (Weidman).

Numerous and often not inappreciable fluctuations have been noted in the relative frequency of many organ cancers in different regions, countries, and races. While the causes of these variations are obscure in most instances, it is usually assumed that exogenous factors are involved in their production.

There exist a few tumors, which display such extraordinarily high discrepan-

cies in their numerical occurrence in various races that a causative racial factor has been considered as the responsible agent, as none of the various exogenous factors examined appeared to be incriminated. Thus, primary carcinoma of the liver is much more frequent in African Negroes, and Asiatic Javanese and Chinese than among members of the white race living in tropical or moderate climates (29 per cent of 359 cancers in African Negroes affected the liver, 57 per cent of all cancers of all Javanese and 30.8 per cent of all cancers in Chinese were liver carcinomas, while only 1 to 5 per cent of all cancers among whites affected this organ) (Shear; Cazanove; Berman; Snijders; Strong and Pitts; Tull; Bonne; and Snijders and Straub). Dietary factors and parasitic hepatic infection do not appear to account for this phenomenon.

It is unlikely that racial factors related to an increased pigmentation are incriminated in this respect. While it is true that Negroes possess the highest production of melanin, which in part enters the blood and is reduced in the liver into a leukoform appearing later in the tubular renal epithelium and in the urine (Jacobsen), and whereas the liver is engaged in the detoxification of aromatic compounds which may give rise to hepatic malignancy, there is no evidence available indicating that a similarly high frequency of primary hepatic cancer exists among American Negroes. It is known that such conditions do not prevail among the American Chinese (5.5 per cent, Ophüls) and among Japanese (2 per cent, Kachi). The recent claim of Des Ligneris, that benzolic extracts of the livers of Bantus possess cancerigenic properties, while those from white individuals are noncarcinogenic, was not confirmed by Kleinenberg, Neufach and Schabad; and Hieger.

The fact that malignant melanomas are apparently much more common among African Negroes than among members of the white races deserves special attention (Sequeira and Vint; Vint; Horgan; Smith and Elmes; Dawson; and Hewer). There are 192 malignant melanomas (10.8 per cent) among the 1,787 malignant neoplasms listed by these investigators. It is scarcely probable that racial factors play a role in this respect, as melanomas are seen relatively rarely among Negroes living in other parts of the world (Hewer). Bauer; MacCallum; and Bishop emphasized the rarity of these neoplasms in American Negroes. A similar statement was made by Butterworth and Klauder. Hewer mentioned that there were observed at the Johns Hopkins Hospital 343 cases of melanomas in white individuals and 10 in Negroes, while the ratio of the white to the colored population of Baltimore was 10:1. It seems to be significant that melanomas occur in colored individuals mainly at sites (sole and nailbed) which are normally nonpigmented (Hardjosoekatmo). The deficiency of pigment thus seems to predispose to melanoma (Hewer). The high incidence of melanomas in white horses supports this contention.

The complete absence of penile cancer among Jews and the relatively frequent occurrence of these neoplasms in other racial stocks (Chinese, 15 per cent of all cancers) gave rise to the claim that the Jews possess a racially conditioned

immunity toward penile cancer (Maresch and Chiari). This concept has been abandoned by the great majority of investigators. This phenomenon among the Jews is related to the practice of circumcision, which prevents the accumulation and decomposition of smegma in the preputial sac and eliminates the carcinogenic mechanism, which seems to play a prominent role among the Chinese and Siamese, in whom these cancers are found frequently associated with phimosis (Wolbarst; Peller; Noble; Ngai; Kennaway and Kennaway; Bercovitz; and Mendelsen and Ellis).

The racial relations of blastomatoid and blastomatous lesions of accidental and occupational genesis appear to have a more definite basis than those of cryptogenetic origin. Keloids are much more common in colored races than in the white race. Solar cancer of the skin represents an outstanding example of a racially conditioned, neoplastic susceptibility of the members of fair-skinned races to the injurious specific action of solar rays, in contrast to the remarkable resistance displayed by the colored races against this agent. The colored races are protected against the action of the solar rays upon the sterols contained in the skin by a heavier pigmentation (Murray).

In addition to the high resistance against actinic cancer of the skin possessed by colored races, particularly Negroes, they are markedly refractory to the carcinogenic effect exerted upon the skin by tar, pitch, and mineral oils (Heller; and Holmes). The natural oiliness of the skin of Negroes seems to protect their skin against the irritative and carcinogenic action of many industrially used chemicals, as occupational dermatitis and cutaneous cancer is rarely seen in Negroes. It is significant in this connection that cancers of the skin are evenly distributed between both sexes in the Negro, in spite of the fact that male Negroes are probably more exposed to environmental carcinogenic influences than white males, who exhibit a marked preponderance of skin cancer over the females of the white race. The racial resistance of the Negroes against tar cancer of the skin does not seem to be of epidermal origin, as cancer of the lip caused by tobacco tar has been found to be much more frequent in Negro women, who indulge more generally in pipe smoking, than in white females (Brewer; and Wile and Hand). Tar cancer of the skin is unknown in Japan in spite of a highly developed coal tar industry. Precancerous hyperkeratotic and cancerous arsenical lesions are also uncommon in Negroes. While it is not likely that racial factors are responsible for the occurrence of cancer of the urinary bladder following a Schistosoma infection among Egyptians only, no plausible reason has been advanced so far as an explanation of this phenomenon.

Similar racial differences in the susceptibility to cancers caused by exogenous agents have been observed regarding animals. Light pigmented cattle, and albino rats and mice have been found to be more sensitive to solar rays and tar than the corresponding dark coated animals. Lynch reported that congenitally hairless mice reacted more rapidly to the carcinogenic action of tar

than normal haired mice. Hueper noted a greater resistance of the skin of hairless rats, in comparison to that of haired rats, to the carcinogenic action of ultraviolet rays.

Since differences in the normal or pathologically produced intensity of melanin pigmentation of the skin have been found to be associated frequently with variations in the relative susceptibility and incidence of various kinds of malignant growths, the question has been raised whether or not these pigmentary conditions play a significant role in the genesis of cancer (Shear).

The intensity of the cutaneous melaninic pigmentation in man is determined in part by a hereditary, racial factor accounting for the occurrence of the variously pigmented human races, and it is partly of acquired nature resulting from the action of numerous endogenous and exogenous factors upon the pigment metabolism of the body. The most common exogenous source of increased pigmentation is represented by solar irradiation, which affects different individuals to a varying degree. While the great majority of persons, including the congenitally colored races, react with a diffuse and homogeneous intensification of the pigmentation (tanning), some individuals, especially the blue-eyed, fair-skinned, and blond or red-haired types, develop, upon exposure to solar rays, a more or less intense burn followed by spotty melanin deposits (freckles) and even localized depigmentations (leukoderma), after repeated and prolonged exposures to such agents. Similar pigmentary cutaneous sequelae are elicited by the external application of roentgen-rays, rays of radioactive substances, and the intravenous injection of larger amounts of thorium-X solutions (Plesch, Karczag, and Keetman). A prolonged and repeated exposure to thermic energy resulting in local congestive changes is followed by melanosis.

The development of a more or less localized melanoderma affecting mainly, but not exclusively, the exposed parts of the skin is observed after a prolonged and usually an occupational exposure to tar, pitch, creosote, anthracene, mineral oil, paraffin, and numerous derivatives of these substances, especially those possessing photosensitizing qualities, such as, aromatic quinone bodies (Wieder; Foerster and Schwartz; Riehl; and Arnstein). A frequent cause of localized diffuse and generalized melanosis is represented by a chronic occupational or therapeutic exposure to numerous inorganic or organic arsenicals (Irgang). Among the numerous less specific exogenous agents producing a localized or diffuse accentuation of the melanin content of the skin, chronic bacterial or parasitic infections and irritations of the skin, accompanied by or resulting in chronic passive congestion (skin in varicose ulcers and chronic universal eczema in beggar's melanosis) may be mentioned.

Localized melanotic disturbances of endogenous origin occur in association with neurofibromatosis, menstruation, and pregnancy (chloasma uterinum). Generalized melanosis of endogenous nature is caused by the destruction of the suprarenal glands (Addison's disease) or the sympathetic plexus of the

abdomen, particularly the solar plexus (acanthosis nigricans). In acanthosis nigricans, hyperkeratoses and verrucous and papillomatous excrescences are found in areas of hyperpigmentation.

The melanosis observed with Addison's disease, as well as beggar's and tar melanosis, may be accompanied by the appearance of pigmented spots in the oral mucosa of white persons, while such pigmentations are normally encountered in Negroes. The chronic ingestion of anthracene cathartics may result in melanosis coli (Bacon and Scheffler; and Jacobsen).

Apart from the occurrence of localized or generalized pigmentary deficiencies (leukoderma and albinism), which are especially frequent in Negroes, the contact with certain aromatic chemicals (hydroquinone bodies) may produce transitory, reversible depigmentations of the skin. More persistent or even permanent leukodermic lesions may result from the prolonged and intensive action of certain chemical and physical agents (tar, solar, and roentgen-rays). It is noteworthy in this connection that the nailbeds, palms, and soles of colored races are normally much lighter pigmented than the rest of the body.

Consideration must be given in this connection to the fact that melanin is a compound possessing a cyclic nucleus (usually of the benzolic type, such as present in the pyrocatechin derivatives; occasionally of the pyrrhol type). While the actual structure of melanin is still controversial and to a certain extent variable, it seems to be generally agreed that when tyrosinase acts on tyrosine, a series of changes in color is set in motion ending in the production of melanin (Jacobsen), which is considered by Gortner to be a true protein (melanoprotein), a conception, which is supported by the antigenic properties possessed by melanin. Greenstein, Turner, and Jenrette stated that melanin is a polymer of undetermined molecular weight, which may readily combine with proteins by virtue of intermolecular attractive forces or by chemical combination.

The aromatic nature of melanin and the quinogenic character of several of its intermediaries might favor the thought of a possible carcinogenic influence, which an increased pigment metabolism may exert locally in the skin or in certain internal organs engaged in the detoxification and excretion of melanin. Nevertheless, this hypothesis receives practically no support from the actual clinical and experimental evidence available at this time. A high physiological pigmentation of the skin, such as found in colored races of the negroid type, has no proven relation to cancer of any organ, if the same conditions of specific or nonspecific exposure (physical and chemical carcinogenic agents and physical or chemical nonspecific trauma) prevail.

An increased pathological pigmentation of the skin is not only a cutaneous reaction common to numerous exogenous and endogenous influences, many of which have no connection with cancerous growths of any kind, but represents also in a certain number of instances a sort of protective mechanism against

carcinogenic factors, such as especially solar rays. It appears probable that the melanotic changes frequently associated with occupational cancerous reactions are causally not interrelated, but merely coincidental.

4. ORGAN AND TISSUE SPECIFICITY

Studies on the experimental production of cancer brought out the fact that there exist marked differences in the susceptibility of various species, different strains of the same species, and different individuals of the same strain to any particular carcinogenic agent. Apart from the spurious species specific differences in sensitivity reported, which may be accounted for by variations in the intensity, duration, and type of carcinogenic exposure, there remain fluctuations in susceptibility. These fluctuations, ranging from relative differences in the length of the latency period to complete refractoriness, must be attributed to other factors, such as differences in the diet, in the thickness of the hair coat and epidermis, in the constitution, and particularly in the metabolic degradation and conjugation of the carcinogenic agents. Shear stated that synthetic carcinogens were found to be active mainly in mice and rats, while other animals, particularly closely related rodents (guinea pigs, rabbits), cats, and dogs, were much less susceptible to these agents or were refractory. A successful experimental production of tumors requires the use of a suitable animal (Putschar; Baumann and Rusch; Lacassagne; Miescher; Sannie, Oberling, and Guérin; Lacassagne and Nyka; Klinke; Kinosita; Woglom; Boyland and Burrows; Lambret, Driessens and Cornillot; Schürch and Winterstein; Haagensen and Krehbiel; Warren; and Menken).

As certain observations made in connection with occupational and experimental cancerigenesis indicated that the various cancerigenic agents seem to elicit neoplastic responses in some organs, but not at all or less readily in others, the claim was advanced that these agents possess well-defined organ and tissue specific affinities (Klinke; Woglom; Bullock and Rohdenburg; Uehlinger; and Evans and Goodman). It was asserted that aromatic amines (dye intermediaries) are attracted by the tissues of the urinary bladder, especially its vasculo-connective tissue elements (Schaer; and Ferguson), while arsenic was said to have an affinity to the epithelial cells of the skin, causing only carcinomatous growths and never sarcomatous tumors (Cook, Haslewood, Hewett, Hieger, Kennaway, and Mayneord).

Uehlinger contended that the rays emitted from radioactive substances could elicit cancerous reactions in some tissues, such as the periosteal tissue, but were ineffective in regard to the lung, brain, and testis. Ilfeld could elicit malignant neoplasms in the kidney, spleen, and uterus of rats and mice into which cholesterol pellets containing 1.2.5.6-dibenzanthracene or 3.4-benzpyrene were placed, while no such responses occurred in the liver, testicle, bone marrow, periosteum, stomach, and brain subjected to the same treatment. Similar observations were reported by Woglom, who inserted threads soaked

in 3.4-benzpyrene into various organs of rats and mice and did not obtain any neoplastic reactions in the kidney, testis, uterus, and liver.

Rusch, Baumann, and Maison found the liver, bone marrow, spleen, testis, and epididymis of rats refractory to 1.2.5.6-dibenzanthracene, and the spleen, submaxillary gland, and liver of rats and the testis and spleen of certain strains of mice unresponsive to 3.4-benzpyrene. These investigators noted that certain types of cells within an organ are more susceptible to neoplastic transformation than other cells, although all have equal contact with the carcinogenic agent. Inasmuch as the ease with which certain carcinogens produce neoplasms in any tissue does not run parallel with the susceptibility of that tissue to spontaneous tumor formation, it was concluded by these authors that the cancerigenic response of a given tissue to a carcinogenic agent is specific both for the cells and the type of carcinogenic agent. An additional example of an apparent selectivity and specificity of a particular carcinogenic agent for a certain organ was thought to be represented by the production of hepatomas in rats by aminoazotoluene, which does not elicit any tumors at the site of application after subcutaneous injection or oral administration (Shear).

This conception appeared to be supported by the fact that dibenzanthracene injected subcutaneously or given orally is excreted through the liver and kidney and appears in the small intestine, without giving rise to cancers in these organs (Branch; Stewart; and Lorenz and Stewart). These observations prompted Woglom to note that the viscera are much less susceptible than the skin and the subcutaneous tissue to tar and synthetic carcinogens, citing Seelig and Cooper; Cook; and Bauer in support of his contention. Nagano as well as Kinosita pointed out that minor changes in the aminoazotoluol and aminoazobenzol molecule may alter the organ specificity and carcinogenic potency of these compounds to a remarkable degree. While aminoazotoluol displays a marked carcinogenic affinity for the liver only when injected subcutaneously, this compound may produce bladder tumors when given orally. Neoplasms of the urinary bladder, but not of the liver, are elicited by 2.3′-dimethylazobenzol and 4′-oxy-2.3′-dimethylazobenzol. 4-amino-benzene and 4-oxyazobenzene, 4:4′-tetramethyldiamino-benzophenone cause gastric papillomas in mice and rats.

A critical evaluation of the evidence, on which the claims of an organ and tissue specificity of the various carcinogenic agents are based, reveals the fact that the results obtained with the individual agents in regard to organ selectivity are far from uniform. Some investigators elicited successfully with certain agents malignant growths in organs which seemed to be refractory to these agents when tested by some other proponent of the specificity theory. Special mention may be made of the experimental cancerigenesis by synthetic carcinogens in the brain, liver, spleen, and kidney. Lorenz and Stewart, for instance, reported subsequently the occurrence of cancers of the small intestine in mice, following the oral administration of one of these agents. Contradict-

ing Uehlinger, who contended that pulmonary, cerebral, and testicular tissue was refractory to radioactive rays, Evans and Goodman noted that lung tissue appears to be about 25 times as sensitive to these agents as osseous tissue, which Uehlinger considered as most susceptible. Recent observations of Andervont have shown that subcutaneously injected aminoazotoluol enhances the development and increases the incidence of pulmonary tumors in mice, exhibiting qualities previously shown as possessed by tar and 1.2.5.6-dibenzanthracene.

Experimental and occupational evidence incriminate tar, pitch, and mineral oil in the production of malignant tumors of numerous organs, such as the skin, lungs, bone marrow, stomach, tonsil, lip, mouth, urinary bladder, and subcutaneous connective tissue. Roentgen-rays have been found responsible for carcinomatous and sarcomatous tissue responses in the following organs: bones, lungs, skin, and bone marrow; while radioactive substances caused malignant tumors in the skin, bones, subcutaneous tissue, lung, liver, bone marrow, and meninges. Solar rays have elicited sarcomas and and carcinomas of the skin and chondrosarcomas of the ear. Arsenic occasionally produced sarcomas of the subcutaneous tissue in man and rabbits (Harbitz; and Cholewa).

The above listing of the different carcinogenic agents of experimental or occupational nature in regard to their various organic neoplastic responses indicates that the alleged organ specificity of these agents is only relative. This conclusion is further emphasized, if consideration is given to the fact that numerous carcinogenic agents are capable of eliciting neoplasms of identical structure in the same organ. Thus, cancer of the skin can be caused by tar, pitch, paraffin, mineral oil, anthracene, creosote, arsenic, solar rays, roentgen-rays, and radioactive substances, while pulmonary malignancy may follow a prolonged contact with radioactive substances, roentgen-rays, chromates, nickel-carbonyl, tar, soot, and asbestos. Neoplastic conditions of the urinary bladder are seen after an exposure to various dye intermediaries, certain finished dyes, tar, paraffin, and certain parasites. Leukemia is caused by the chronic action of benzol, radioactive substances, roentgen-rays, tar, and various synthetic carcinogens.

There exists sufficient and reliable evidence indicating that several fundamentally different carcinogenic agents may summate their action upon an exposed tissue, causing a hastening of the neoplastic response. Such observations have been made in connection with the combined exposure to two of the following agents upon the skin: tar, arsenic, solar rays, and roentgen-rays.

It seems to be a general principle that cancerous growth ensues most likely at those sites where the carcinogenic agent is present in an optimal concentration and for the most prolonged period. The site, amount, and intensity of exposure, the speed of resorption of the carcinogenic agent at the site of primary contact, the organs of deposition, of metabolic conversion and of excretion, in addition to the character of the metabolites formed, and only excep-

tionally a certain organ affinity of a particular carcinogenic substance, such as displayed for instance by the estrogenic hormones, represent the factors which determine mainly the location of the neoplastic response to a given carcinogenic agent.

The relatively rapid resorption of o-aminoazotoluol and beta-naphthylamine from the site of subcutaneous injection may account in part for the absence of tumor formation in the subcutaneous tissue and for the appearance of neoplasms in the liver and bladder, respectively, where these chemicals are either metabolized or excreted (Brock, Druckrey, and Hamperl; and Hueper). This conception is supported by the fact that in the case of aniline tumors, neoplasms are frequently observed in the upper portions of the urogenous tract (the ureter, renal pelvis, and kidney), and occasionally cancers of other organs, such as the pancreas and skin, are found in association with bladder tumors. Recent experimental studies of Shear and Stewart with subcutaneously introduced, nitrogen-containing, benzene derivatives, including those of an aromatic amine type, showed that once in a while mice develop cancerous responses at the site of injection or in some internal organs other than those of the urogenous tract.

Observations, which support this conception of the causative mechanisms underlying the localizations of cancers, have been made in connection with the experimental carcinogenesis by various synthetic carcinogens as well as tar. Andervont noted that the subcutaneous injection of 1.2.5.6-dibenzanthracene into mice was followed by a larger number of pulmonary neoplasms when this chemical was dispersed or dissolved in a vehicle which is quickly resorbed (horse serum), than when it is introduced in a vehicle which remains over a prolonged period at the site of injection (lard and cholesterol). Lettinga obtained similar results, when he increased the amount of 1.2.5.6-dibenzanthracene injected subcutaneously above a certain level, where pulmonary neoplasms became a frequent occurrence due to an increased resorption into the organism of the carcinogen introduced in excess. Peacock and Beck reported that the formation of sarcomas in mice following the injection of 3.4-benzpyrene depended upon the rate of resorption and excretion. While mice, which eliminate this chemical within three months, rarely exhibited neoplasms, those animals which retained the substance beyond six months frequently developed sarcomas. Numerous carcinogens produce epitheliomas when applied externally to the skin, and elicit sarcomas when injected subcutaneously.

Mention may be made finally of the rate of elimination of a given carcinogen from the organism, as a factor possessing a definite significance concerning the occurrence and localization of a neoplastic effect. Chalmers and Peacock recorded that carcinogenic, polycyclic hydrocarbons injected intravenously are excreted with the bile within 6 to 8 hours later as water soluble compounds. Berenblum and Kendall noted that intraperitoneally introduced 1.2.5.6-dibenzanthracene disappears from the body within three weeks. Brock, Druck-

rey, and Hamperl stated that 3.4-benzpyrene injected into rats was demonstrable in organs rich in lipoids six months after its administration.

It is evident from these data and considerations that the alleged organ specificity of carcinogenic agents is actually a highly complex phenomenon, depending upon a number of factors varying in intensity and nature and representing rarely a genuine tissue affinity.

5. PRIMARY MULTIPLICITY OF TUMORS

The pluricentric genesis of tumors is a phenomenon often observed in connection with occupational neoplasia, which presents an especially favorable medium for the study of the various types and the different and in part controversial aspects of blastomatous multiplicity. It is pertinent that a discussion of this problem must be limited to the generally recognized neoplastic growth manifestations, excluding a number of often multiple, benign, tumor-like, cellular proliferations of hyperplastic character, such as infectious epithelioses of the skin (condylomata, warts, and molluscum contagiosum), certain granulomas (xanthomas, giant cell granulomas, epulides, nasal polyps, and keloids), some nodular, more or less circumscribed, adenomatoid, compensatory or hormonal hyperplasias (thyroid, breast, uterus, and prostate), and several congenital tissue malformations and misplacements (pigmented and angiomatous nevi, accessory spleens, and aberrated foci of suprarenal tissue), which frequently coexist with true tumors. Primary multiple neoplasms may be classified according to the following viewpoints:

1. Genesis: a) Congenital multiplicity: affecting primarily either one system (neurofibromatosis, myelomas, and multiple enchondromas) or several organ systems (rhabdomyomatosis of the heart associated with gliomas of the brain, adenomas of the kidney, and epitheliomas of the skin); developing secondarily on the basis of a congenital and/or hereditary predisposition, probably under the influence of an exogenous factor (multiple adenomatous polyposis and carcinosis of the intestine and multiple epitheliomatosis of the skin in xeroderma pigmentosum).

b) Acquired multiplicity: caused by occupational, environmental, or experimental exogenous factors of physical or chemical nature, or by endogenous, hormonal, or other influences.

2. Biological Character: a) Multiple benign blastomatosis (most frequent), such as adenomatosis of the prostate, breast, thyroid, ovary, intestine, salivary glands, and liver; papillomatosis of the urinary bladder, larynx, nasal passages, and mammary ducts; epitheliomatosis of the skin; and myomatosis of the uterus.

b) Multiple malignant blastomatosis (most often observed in the skin, liver, intestine, bladder, and prostate).

c) Multiple benign and malignant blastomatosis.

3. Histological Character: a) Multiple neoplasia of structurally identical tumors.

b) Multiple neoplasia of structurally divergent tumors.

4. Histogenesis: a) Neoplastic multiplicity of one germinative layer.

b) Neoplastic multiplicity of several germinative layers.

5. Localization: a) Organic multifocal neoplasia.

b) Systemic multifocal neoplasia.

c) Nonsystemic, heteroorganic, multifocal neoplasia.

6. Arrangement: a) Symmetrical multiplicity (skin) or multiplicity in paired organs (ovary, testes, breast, kidneys, and lungs).

b) Asymmetrical multiplicity.

7. Time: a) Synchronous multiple tumor formation.

b) Metachronous or successive multiple tumor formation.

The establishment of the presence of multiple benign or of multiple benign and malignant tumors is relatively readily made. Great difficulties may be encountered in the case of multiple malignancies, as the possibility of multiple foci by direct extension or by metastatization must be definitely excluded.

Billroth (1869) set up the following postulates for the establishment of the authenticity of primary multiple cancers: 1. Each tumor must have an independent histological appearance; 2. the tumors must arise in different locations; and 3. each tumor must produce its own metastases. Numerous subsequent investigators of this problem voiced various objections against these demands, which were considered to be not only too strict, but in an appreciable number of cases misleading (Seecof; Goetze; Schreiner and Wehr; Warren and Gates; Hanlon; Hurt and Broders; and König).

Warren and Gates adopted the following stipulations: Each tumor must give a definite picture of malignancy; each must be distinct; and the probability of one being a metastasis must be excluded. Goetze was prompted to suggest that the criteria of neoplastic multiplicity of malignant type should be as follows: "The macroscopic and microscopic appearance of the tumors must be that of the usual carcinomas of the organs involved; exclusion of metastases must be certain; diagnosis must be confirmed by the character of metastases in each case."

Seecof raised against Billroth's postulates the following objections (Kretschmer):

1. Difference in histological appearance: a. The presence merely of different histological appearance is of little value because of the possible change of cell type in metastases and in regional or local recurrences, especially after biopsy or treatment; b. the absence of different histological appearances may be of little value on the negative side, because in "system" and "paired organ" instances there may be multiple foci with the same type cell.

2. Different points of origin: a. That they are found in different locations may be of little value because of possible error in misjudging a metastatic focus in an apparently definite case, especially when the change in type cell is marked; b. in the absence of different locations a case might well be ruled out

were it not for the group of mixed tumors, the so-called sarcocarcinomata, a much disputed group.

3. Each must produce its own metastases: a. When each primary focus produces its own metastases the case is definitely one of multiple primary neoplasms; to prove that the second apparently primary focus is not a "changed" metastasis from the first may not be possible in a given case by our present methods. b. Multiple primary malignant tumors may exist without demonstrable metastases.

These considerations and a markedly increased knowledge of tumors and of neoplastic multiplicity, particularly of occupational and experimental genesis, have led to a considerable liberalization of the postulates of Billroth during recent times, resulting in a more frequent recognition of multiple primary cancers.

The data concerning the incidence of primary neoplastic multiplicity differ considerably depending upon the fact, whether both malignant and benign tumors were considered by the particular investigator, who sometimes included even congenital malformations and blastomatoid hyperplasias among the "neoplastic" conditions, or whether exclusively primary multiple cancers were made the subject of a statistical analysis. Additional variations in the figures obtained are introduced by the type of material evaluated. Information based on clinically observed cases deals mainly with tumors located at accessible sites, such as the skin and those mucous membranes open to direct inspection. Statistical data obtained from post-mortem examinations contain to a much more extensive degree multiple tumors situated in internal organs, while they lack to some extent the proper proportion of multiple neoplastic reactions involving accessible sites, because of successful therapeutic removal of some of these manifestations during life. The great majority of cases of multiple neoplasms of internal organs are necropsy findings, as the differentiation between primary multiple growths and secondary metastatic multiplicity can be made with safety usually only at autopsy, which sometimes yields evidence of primary neoplastic multiplicity, where such a condition is not suspected during the lifetime of the patient, because of the small size of one of the primary growths or of the absence of histological studies.

The incidence of primary neoplastic multiplicity of benign and malignant tumors, including blastomatoid conditions, such as prostatic hyperplasias, goiters, and pigmented and angiomatoid nevi was 14.4 per cent of all tumor cases observed at autopsy from 1903 to 1924 by Puhr, who noted that this figure varied between 23.52 and 12.69 per cent for the years 1921 to 1924. Holmqvist and Nelson, using the same standards as Puhr, recorded an incidence of neoplastic multiplicity amounting to 40 per cent of all tumor cases found among 4,000 autopsies, of which 55 per cent showed the presence of some kind of neoplasm. Egli reported a frequency of multiple tumors in 27.2 per cent of necropsies exhibiting blastomatous conditions.

The statistical data dealing with multiple primary malignant growths display similar variations. Puhr recorded an incidence of 0.3 per cent of primary malignant multiplicity among cancer cases of his series; Holmqvist and Nelson gave an incidence figure of 1.2 per cent; Warren and Gates, 1.84 per cent (of a series of cases collected from the literature) and 3.7 per cent (of a series of American cases); Goriainowa and Schabad, 1.4 per cent; Egli, 2.07 per cent; Harbitz, 3.24 per cent; Schreiner and Wehr, 2.7 per cent; Bugher, 3.1 per cent; Burke, 7.8 per cent; König, 1.4 per cent; Firket, Chevremont, and Dardenne, 1.15 per cent (nonsystemic multiple cancers only); Hummel, 1.1 per cent; Hartmann, 1 per cent; Murray, 1 per cent; Sikl, 0.89 per cent; Müller, 1.69 per cent (nonsystemic multiple cancer cases only); Gade, 0.76 per cent; Billelo and Montanini, 0.5 per cent; Regaud, 2.1 per cent; Tiemann, 1.67 per cent; von Hansemann, 0.5 per cent; Junghanns, 0.45 per cent (nonsystemic multiple cancers only); and Kirshbaum and Shively, 1.77 per cent, while Beck noted a primary systemic multiplicity in 19 per cent of a large series of cutaneous epitheliomas.

The comparative value of many of these data is impaired by the fact that no distinction has been made between systemic and nonsystemic multiplicities. Special mention may be made in this connection of an observation reported by Hurt and Broders, who noted that in a series of 2,124 cases of histologically established malignant tumors second primary neoplasms developed within two years in 71 cases or in 3.4 per cent of the cases.

Similar findings as to the occurrence of primary multiple tumors were made in domesticated animals. Goodpasture and Wislocki reported the existence of multiple, usually benign, tumors in all of 15 old dogs studied at autopsy. This observation was confirmed by Cohrs who found in 26 out of 70 dogs examined (37.14 per cent) multiple neoplasms, which are rarely noted in young animals (Pack and LeFevre).

The statistical data presented show that more recent investigations yielded a higher incidence of primary multiplicity of cancers than that recorded previously. European statistics give in general distinctly lower figures than those reported from America. The reasons behind these discrepancies are not entirely clear. It may be possible that local differences in the interpretation of histological observations, in the thoroughness, and in the routine procedure of the microscopic study of post-mortem material may play a certain role in this respect (Burke; and Warren and Gates). These discrepancies might reflect fluctuations and variations in the intensity of exposure to and the nature of exogenous carcinogenic factors active at different times and in various regions.

Systemic neoplastic multiplicity is often found in cancers of the liver, lung, intestine, stomach, and ovary (14 to 17 per cent), according to Goriainowa and Schabad, while it is of medium order in cancers of the uterus and esophagus (7.1 per cent), rare in regard to cancers of the skin (4 per cent), and absent as to cancers of the mouth, tongue, pharynx, and larynx. It is obvious that

these figures, given by Goriainowa and Schabad, do not conform to the observations made by other investigators. A primary multifocal origin of neoplasms of the urogenous tract, particularly of the bladder, is present in an appreciable proportion of cases (approximately 25 per cent of bladder tumors). The relatively high incidence of primary multiple cancers of the skin is a well established fact (Beck; Schreiner and Wehr; Owen; and Hanlon). Drooker mentioned the not infrequent occurrence of multiple primary cancers of the larynx, while Welsh noted the same phenomenon in regard to prostatic malignancies.

Nonsystemic, primary, multiple malignancies are less often observed than those of systemic character. Such heteroorganic, nonsystemic, neoplastic combinations are said to involve especially frequently both the skin and alimentary tract. While Kretschmer maintained that neoplasms of the urogenous tract are found rarely in association with cancers of other organs, Eisenstaedt as well as Kirshbaum and Shively commented on the frequent occurrence of such combinations, particularly in regard to the gastro-intestinal tract. Additional instances of the coexistence of cancers of the urogenous tract with those of other organs (skin, pancreas, scrotum, stomach, lung, prostate, ear, and colon were reported by Kretschmer; and Hueper).

Sex does not seem to play any important role in the causation of neoplastic multiplicity of most organs with the exception of the female sex organs. Multiple epitheliomas of the skin are found more often in men than in women, but these tumors are in general more common in the male than in the female. Desaive, Firket, Chevremont and Dardenne mentioned the absence of any differences in the sex distribution of multiple, nonsystemic cancers. Similar observations were made by Hurt and Broders.

Warren and Gates found in their American series of 40 cases that the female sex was involved 25 times and the male sex, 15 times, a sex relation confirmed in general by Holmqvist and Nelson, while Burke as well as Kirshbaum and Shively noted a preponderance of about 2 to 1 of the males over the females.

Holmqvist and Nelson; and Hanlon expressed the opinion that the incidence of multiple malignancies increased with age and that this condition was met most often in individuals of advanced age. Warren and Gates maintained that such a statement is based on inadequate data and that the age at which multiple cancers are found is approximately the same as in cases with single tumors. In support of their contention, Warren and Gates cited the following age figures: The average age of cases of multiple cancers was 61.8 years against an average age of 55.5 years of individuals with single cancers; the average age of 83 cases of three or more malignancies was 57.9 years for the 51 males and 47.8 years for the 32 females; the average age for the entire series being 54.0 years. Warren and Gates commented that "certainly these cases have not developed their multiplicity of cancers because of a longer time during which

additional tumors might make their appearance." Hanlon found an average age of 63.6 years for cases with three or more malignancies.

While general agreement exists concerning the causal significance of genetic factors for multiple malignancies occurring as a rule during the early periods of life (congenital neoplastic multiplicities), a controversy prevails concerning the etiology of the multiple primary cancers observed during the adult parts of life. Ewing as well as Orr are of the opinion that the occurrence of multiple cancers can be explained on the grounds of mere coincidence. Hanlon asserted that multiple malignancies represent incidental phenomena rather than a definite response to any law of neoplastic formation. This conception is opposed by Warren and Gates; Hurt and Broders; and Hartmann, who pointed out that multiple cancers are observed more frequently than can be explained on the basis of chance, implying that definite factors must be operative in bringing about such multiple neoplastic manifestations.

Rössle expressed the belief that in cases of a neoplastic multiplicity a special weakness of the connective tissue existed. Puhr considered the presence of a special constitutional disposition as a causative factor for those cases associated with hamartias and choristias. Rössle as well as Bartel opined that such neoplastic multiplicities may be related to hereditary tendencies, such as those present in tumor families. Hurt and Broders noted that the family histories in most clinical cases of neoplastic multiplicity lacked detail and thoroughness, and were decidedly inadequate for any statistical analysis concerning hereditary influences. Hurt and Broders mentioned that there was some record of a family history in 70 of their cases, and that a history of malignancy in other members of the family was recorded in twenty cases (28.6 per cent). Apart from the fact that such data are notoriously unreliable, such a figure must be considered as being without any significance because normally about 10 per cent of all adults die from malignant tumors.

Holmqvist and Nelson contended that the factors prevailing in cases of primary multiplicity of tumors justify the assumption of a probably genetically conditioned, neoplastic diathesis of local or general nature. These investigators noted that sexual endocrine disturbances might furnish such a constitutional predisposition, especially in regard to multiple neoplasms occurring in women. There exist, according to their speculations, individuals possessing a tendency toward malformation only, while a second group of individuals exhibit a predisposition to develop exclusively benign tumors, and malignant tumors are only encountered in a third group of individuals. Warren and Gates proposed that the appearance of multiple cancers might indicate the presence of a predisposition of unknown nature. Welsh suggested that the congenital predisposition might be of biochemical nature, consisting, for instance, of a deficient pigmentation and thereby conditioned increased susceptibility to the carcinogenic action of solar rays, or resulting from endocrine disturbances or

hormonal adjustments causing primarily compensatory adenomatoid overgrowths, some of which ultimately assume malignant characteristics. Kirshbaum and Shively claimed that some persons may be endowed with a congenital or acquired predisposition toward tumor formation of multiple type.

Desaive, Firket, Chevremont, and Dardenne maintained that a neoplastic multiplicity does not indicate necessarily a congenital general predisposition, but rather that the affected individuals were exposed to various exogenous carcinogenic agents. A similar interpretation may be attached to a statement of Burke, who noted that any factor producing an increase in single cancers is bound to cause at least a corresponding increase in multiple cancers.

The observations made in this matter in connection with the occupational and closely related, experimental cancerigenesis demonstrate clearly the importance which exogenous carcinogenic factors possess for the production of systemic and nonsystemic multiple primary cancers. It is obvious that a prolonged and extensive exposure to strongly cancerigenic agents is the main cause of such multiple neoplastic reactions, which do not exhibit in many instances any definite relations to constitutional or genetic factors. A systemic neoplastic multiplicity is observed in 15 per cent of the industrial arsenical epitheliomas, in 20 per cent of the tar cancers of the skin, in 15 per cent of the paraffin and oil epitheliomas, in 25 per cent of the aniline cancers of the bladder, and in 30 per cent of the roentgen-cancers of the skin. An excessively high incidence of multicentric cancerigenesis exists in connection with osteogenic sarcomas and pulmonary carcinomas caused by radioactive substances. The occurrence of nonsystemic, cancerous multiplicity was observed after an industrial exposure to various agents, such as tar, aromatic amines, paraffin and mineral oil, and radioactive substances, furnishing additional evidence supporting the causal role of exogenous factors in the production of neoplastic multiplicities of different types.

The age distribution of multiple cancers, and the relatively frequent association of cutaneous and gastro-intestinal cancers or gastro-intestinal malignancies and urogenous tumors favor a causal role of extraneous agents. This is because a cutaneous exposure to chemical carcinogens is usually accompanied by a simultaneous ingestion of such agents and, correspondingly, the introduction of carcinogenic material into the alimentary system is often followed by the excretion of this material through the urogenous tract.

Similar and supporting evidence is supplied by observations made in connection with the experimental production of cancers by chemical and physical agents [solar rays, roentgen-rays, radioactive substances, tar, pitch, aromatic amines, and synthetic polycyclic synthetic hydrocarbons (Reinhard and Thibaudeau; Twort and Ing; Shear; Andervont; Hueper, Wiley, and Wolfe; and Putschar and Holtz)]. These experimental studies demonstrate that these agents are not only capable of eliciting systemic, multiple neoplastic responses unrelated to hereditary, blastomatous tendencies, but that they may stimulate

directly or indirectly predisposed foci located in remote organs, such as the lung, into active neoplastic proliferation causing a nonsystemic neoplastic multiplicity. An identical effect may be elicited by the introduction of excessive doses of certain carcinogenic chemicals into the subcutaneous tissue, from where an overflow of carcinogenic material may incite multiple malignant growths in remote internal organs, such as the lung or liver (Andervont; Shear; Lettinga; and Lynch), in addition to the cancers appearing at the site of primary contact.

The observations made in connection with occupational and experimental, neoplastic multiplicity demonstrate the fact that the exogenous carcinogenic agents can produce the various types of multiple tumors mentioned in the classification of these growth manifestations. The evidence presented suggests strongly that more consideration must be given in the future to the causative role which extraneous factors may play in the development of primary multiple neoplasia.

This localistic conception of the action of carcinogenic agents in connection with the occurrence of nonsystemic multiple cancers is of fundamental significance. Murray; Cramer; and Peller recently contended that the presence of a cutaneous malignancy counteracted the development of a second primary malignancy in certain internal organs. Murray as well as Cramer claimed that such an antagonism existed between the experimental cutaneous tar cancer and the spontaneous mammary cancer of mice, and that for this reason the coexistence of a mammary cancer and a skin cancer is rare.

Peller maintained that the occupational contact with tar, while increasing the incidence of skin cancer as well as that of gastro-intestinal, hepatic, and vesical malignancies, lowered the frequency of cancer of the lip, tongue, and esophagus. Similar antagonistic interrelations were claimed to exist between solar epitheliomas of the skin and the liability to cancers of the internal organs. Peller suggested that the presence of a relatively easily curable external cancer of the skin might protect against the acquisition of a much more dangerous malignancy in some internal organ. Peller asserted that such a systemic interaction accounted for the statistically demonstrable rarity of internal cancers among the personnel of the United States Navy. Cramer contended that this mechanism offered a plausible explanation for the fact that the populations of different regions show statistically approximately the same total incidence of cancer in man with a widely varying frequency in the proportion of different organ tumors.

Reports from the International Labour Office state that it is a curious fact that nearly all occupations noted for excessive skin cancer mortality also record a cancer mortality for sites other than the skin in excess of the average. Conrad and Bradford, analyzing the same occupational cancer mortality statistics used by Peller (England and Wales for the years 1921-1923), were unable to substantiate the claims made by this investigator. On the contrary,

although numerous exceptions occurred, there was on the average a slight direct association, as occupations in which there was a relatively high skin cancer and lip cancer rate tended to show, also, an excess of cancer of other sites. Observations made by Southam; Sladden; Roesch; and Bonser and Connal confirm this observation in the occupational cancer field.

The claims of Murray and Cramer were not confirmed by Bonser and Connal. The numerous experiments made with tar and various synthetic carcinogens applied to the skin or injected subcutaneously have demonstrated, beyond any doubt, that the presence of a cutaneous malignancy does not prevent the development of a similar reaction in some internal organ (Bogen and Loomis; Schabad; Lynch; and Andervont).

The statistical interrelations observed by Peller represent misinterpretations of unrelated data, as this investigator neglects entirely to consider any differences which may be present in the type and intensity of exposure to various carcinogenic exogenous agents probably present in the groups subjected to a statistical analysis.

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XIII

THE RELATION OF OCCUPATIONAL NEOPLASIA TO THEORIES OF CANCERIGENESIS

1. CONSIDERATION AND CLASSIFICATION OF THEORIES

BRIEF references were made frequently in preceding chapters to the relation of various types of occupational neoplasms to different theories of carcinogenesis. The inadequacy and the contradictory nature of the conceptions held represent a factor which is apt to influence seriously the general attitude toward the cancer problem, especially the aspects connected with the technical, hygienic and medical measures of preventive and prophylactic type. Inasmuch as an effective future control, not only of occupational cancers but also of cancerous growths in general, depends to a not inconsiderable degree upon a proper appreciation of the causes and causative mechanisms that produce these disorders, a comprehensive analysis of the relative merits of different theories of carcinogenesis, with due consideration of data supplied from a study of occupational tumors, appears to be pertinent and valuable.

The numerous theories which have been advanced to explain the phenomenon of the malignant neoplastic growth may be placed in one of the following two main groups:

I. Theories based on morphological studies and relating to the formal genesis of cancers.

1. Cohnheim's theory of cancerigenesis from embryonic, misplaced cellular foci.
2. Ribbert's theory of cancerigenesis from groups of differentiated cells which became detached during fetal or postfetal life from their normal environment.
3. Virchow's theory of cancerigenesis from cells chronically irritated or stimulated by inflammation producing agents.
4. Tissue senescence theory of cancerigenesis from cells undergoing physiological or pathological atrophying, senile changes.

II. Theories based on biological cellular changes and relating to the causative genesis of cancers.

1. Theories considering cancerigenesis as the result of a direct action of a physical or chemical agent upon some component part of a cell or groups of cells, whereby the agent may be of animate or inanimate nature and of endogenous or exogenous origin.
2. Theories regarding cancerigenesis as the result of a specific disturbance

of some special phase of the cellular metabolism (Warburg; Hammett; Waldschmidt-Leitz; and Koegl).

3. Theories considering cancerigenesis as the product of a cellular mutation of inherited, congenital, or acquired origin.
4. Theories incriminating viruses in the development of cancers.

2. COHNHEIM'S AND RIBBERT'S THEORIES

The theory of Cohnheim, which is based on the assumption that there occur in all organs accessory, misplaced foci of embryonic cells having become detached from their normal environment and cellular contacts during embryonic life, contends that such embryonic cellular germs possess a special proliferative potency which may give rise to neoplastic formations. Ribbert extended this conception to groups of fully differentiated cells, which had lost during fetal or postfetal life their normal connections and which had maintained favorable nutritive conditions. It must be conceded that there occur benign and malignant, blastomatoid and blastomatous formations, which originate evidently from misplaced embryonic cells and which affect most often certain tissues and sites favoring such embryonic cellular aberrations [dermoids, teratomas, and mixed teratoid tumors of the ovary, testis, and retroperitoneal space and their malignant complications; dysontogenetic tumors of the urogenital region; cysts and neoplasms originating from the omphalomesenteric duct (enterocystomas), from the urachus, from the hypophyseal duct, and from branchiogenic clefts; chordomas; retinal and suprarenal neuroblastomas; angiomas; and hereditary and multiple enchondromas]. But the fact remains that such occurrences are relatively rare, particularly in regard to the malignant sequelae, and are not the common outcome of embryonic misplacements as exemplified by the frequent existence of accessory spleens, thyroids, parathyroids, suprarenals, and pancreas. It is uncertain whether such misplaced embryonic anlagen actually possess a higher reactivity than normal cells, which favor their transformation from dormant embryonic cells into malignant ones upon the intervention of some additional factor, such as chronic irritation, exogenous trauma, or vascular disturbance. In view of the inability to demonstrate such embryonic foci as the neoplastic source in the great majority of tumors, some investigators advanced the supposition that all tissues are studded with very small foci of embryonic cells. These cells, which cannot be visualized with the existing methods, allegedly furnish the germinative foci of cancerous growths when properly stimulated. Such speculations unsupported by any definite facts are obviously without any value.

Similar objections can be raised against the theory of Ribbert. Benign traumatic tissue misplacements furnish only exceptionally the basis of benign or malignant neoplasms. Cellular heterotopias, accompanying infiltrative, epithelial hyperplasias of a chronic inflammatory origin or characterizing endometriotic manifestations, lead only relatively rarely to malignant growths.

Apart from these considerations unfavorable to the misplacement theories of cancerigenesis, the fact remains that neither the embryonic character nor the misplacement of embryonic or adult cells can explain plausibly the tendency toward an extraordinary proliferation and an atypical and neoplastic growth, which such cells are claimed to possess. These conclusions are confirmed extensively by observations made in connection with the morphological phenomena associated with occupational and related experimental cancerigenesis. The histological studies of such lesions show unmistakably, especially during the precancerous stage, that cellular alterations of preneoplastic and neoplastic type are often multifocal or sometimes even more or less diffuse. This excludes the possibility that preformed, germinative, embryonic cell foci form the anlagen of the cancers observed.

3. VIRCHOW'S THEORY

Similarly weighty objections may be raised against the chronic irritation theory of cancerigenesis of Virchow and its regenerative modification proposed by Fischer-Wasels (Roussy). Chronic inflammatory changes, often associated with prolonged and disturbed regenerative cellular proliferations, sometimes of metaplastic nature, are frequently found in a tissue from which cancerous growths originate. Regardless of this, the succession and co-existence of such cellular phenomena represents by no means a conclusive proof for the actual presence of a causal relationship. The chronic inflammatory conditions characterizing the large number of occupational dermatoses and certain chronic pneumoconioses are not significantly related to the occurrence of malignant tumors in these organs (Oppenheim; and Leitch).

Attention may be called to the fact that carcinomas of the male urethra, which is frequently the site of a chronic gonorrheal inflammation, are extremely rare [only 145 cases of carcinoma of the male urethra on record (Kreutzmann and Colloff)]. Similar conditions prevail in regard to the frequency of primary carcinoma of the Fallopian tube, which perhaps is even more affected by chronic inflammatory processes than the urethra, but which is equally rarely involved by malignant growths [239 cases reported up to 1930 (Gallagher; Holland; and Johnson and Miller)]. Chronic sinusitis, a rather common disease, is another chronic inflammatory disorder relatively rarely giving rise to cancer. Mention may be made of the comparatively low incidence of carcinoma of the cervix in a completely prolapsed uterus, which is exposed to all kinds of bacterial, physical, and chemical irritations and injuries (Högler). The actually minor etiological significance of chronic irritation in the production of cancer is indicated furthermore by the fact, that the transformation of the relatively frequent condylomata acuminata, which are eminently proliferative benign irritative lesions, into carcinomatoid or carcinomatous manifestations is evidently extremely rare (Buschke; Buschke and Loewenstein; Israel; Frei; and Mühlpfordt). Chronic, dysenteric, polypous

colitis represents only exceptionally a basis of an intestinal malignancy, while the intestinal polyposis of noninflammatory and noninfectious origin is complicated in most instances by cancerous growths. Whereas chronic cystitis is a condition more commonly existing in women than in men, cancer of the bladder shows a reverse sex relation.

Finally, metaplastic changes can scarcely be rated as frequent precancerous lesions without distinct reservations. While leukoplakias of the oral mucosa, especially of the tongue, exhibit a certain tendency toward a malignant transformation, this is very much less pronounced for similar lesions present in the esophagus, stomach, and intestine. Similarly, the metaplastic osseous tissue formed in myositis ossificans does not display any predisposition toward a malignant transformation in spite of frequent traumatization.

Corresponding observations are available from the field of experimental carcinogenesis. The pulmonary neoplasia elicited in mice by the subcutaneous introduction of certain synthetic carcinogenic chemicals is characterized by the complete absence of inflammatory reactions (Andervont; Grady; and Grady and Stewart). Similar observations were reported by Hueper in connection with the experimental production of "aniline cancers" in the bladder of dogs, and by Page in relation to the epidermal and cutaneous changes elicited in the skin of mice painted with methylcholanthrene and cholanthrene. "Spontaneous" mammary cancers occurring in mice are regarded by Regaud as well as Loeb as typical examples of carcinogenesis on a noninflammatory basis.

4. SENESCENCE THEORY

The senescence theory of cancerigenesis, which assumes that during the phase of physiological tissue senescence, characterized in general by a prevalence of catabiosis and cellular atrophy, there develop multifocal, anabiotic, cellular proliferations throughout the body in various organs and tissues, which may proceed, after passing through a stage of blastomatoid hyperplasia, to the formation of cancers (Feyrter). The neoplastic action of exogenous or endogenous agents upon the tissues of young individuals is explained by this theory as the result of an artificial precocious aging of the particular exposed tissue, which finds its morphological expression in the appearance of fibrosis and in the reduction of vascularity. It seems probable that the disturbances in the hormonal balance accompanying the aging process may be the cause of hyperplastic proliferations in certain organs (prostate and mammary gland) observed frequently during more advanced adult age. These proliferations may prepare the soil for a subsequent cancerous development. It appears also possible that a senile hormonal imbalance may activate some dormant cancerous process of endogenous or exogenous origin.

No doubt this factor is without any appreciable practical significance in the causation of occupational cancers as shown by the data reported on the age distribution, exposure time, latency period, and preparatory anatomical lesions

of these neoplasms. It may be pointed out that the senile tissue changes (fibrosis, atrophy, and reduced vascularity) cause an insufficient cellular nutrition, which favors cellular differentiation and proliferative arrest rather than the development of any dedifferentiated, cellular growth manifestations. The histological investigations of numerous occupational, nonoccupational, and experimental precancerous conditions have shown unequivocally that a multifocal appearance of vascular proliferation and hyperemia precedes or accompanies precancerous and cancerous growths (Guldberg; Ulesco-Stroganova; Bang and Guldberg; Hueper; Ferguson; Thiessen; and Fansler), providing thereby an appropriate nutritive background. The atrophic and fibrosing lesions, co-existing frequently with the hyperplastic ones in precancerous conditions, usually do not furnish the basis for neoplastic reactions.

The inadequacies of the various theories of the formal genesis of cancers are attributable to the fact that they are based mainly upon morphological criteria and their postulated relationship to malignant growth processes, and that they disregard entirely the fundamentally more important aspects of the specific or nonspecific causation and causative mechanism of these phenomena as well as the intrinsic characteristics of malignant cells. These considerations led to the establishment of numerous theories on the causal genesis of cancers.

5. CHEMO-CYTOTOXIC THEORIES

The claim was recently advanced that the primary action of carcinogenic agents, especially the synthetic chemical carcinogens, is a cytotoxic, degenerative one, resulting in an inhibition or retardation of cellular proliferation rather than a growth stimulation. The carcinogenic effect was said to be a secondary one, becoming manifest only after new cells had been formed which were able to resist the specific inhibitory action of the carcinogens (McJunkin and Wolavka; Haddow and Robinson; Haddow; Haddow, Scott, and Scott; Earle and Voegtlin; and Wolbach). This contention is based upon the demonstration of a retardation of the growth of normal young rats when treated with one of the several synthetic, carcinogenic hydrocarbons (1.2.5.6-dibenzanthracene) (Haddow; Haddow, Scott, and Scott; and Lees), and of that of normal chick fibroblasts when grown in a culture medium containing methylcholanthrene (Earle and Voegtlin). Chemically related hydrocarbons did not exert such effects upon the growth rate of normal cells.

Additional support for the thesis of a primary cytotoxic effect of carcinogens was thought to be provided by observations made in connection with their effect upon proliferative activity and vitality of malignant cells. Haddow and Robinson recorded that the administration of 1.2.5.6-dibenzanthracene, 3.4-benzpyrene, or 5.6-cyclopenteno-1.2-benzanthracene to rats carrying Jensen or Walker tumors caused a considerable inhibition in the rate of growth of these neoplasms. Pybus and Miller obtained similar results, i.e. partial or complete regression of spontaneous mammary cancers in mice after an intra-

peritoneal injection of 1.2.5.6-dibenzanthracene. McJunkin and Wolavka, who used rats bearing transplanted sarcomas, observed in all animals a complete regression of these neoplasms after an intratumoral injection of emulsions of 1.2.5.6-dibenzanthracene in lecithin. Such an effect was noted in two-fifths of a series of tumor-bearing rats which received the carcinogen emulsion into the peritoneal cavity. These investigators suggested that the carcinocidal action exerted by carcinogens may not be a primary one, but may be caused by a reactive production of large amounts of factors slowing cellular proliferation.

Similar experiments undertaken by Lees on transplanted tumors, which were injected with 1.2.5.6-dibenzanthracene, resulted in a marked reduction in the growth rate of these neoplasms and a considerable loss of weight of the treated animals, indicating that such chemicals affect both normal and neoplastic cells in the same manner. These observations were confirmed by Morelli and Guastalla, who employed rats with Jensen's sarcoma and Walker's carcinoma in their experiments. The intratumoral injection of 3.4-benzpyrene caused a necrosis of the neoplastic tissue. This effect was less marked, when the carcinogen was introduced at a point remote from the tumor. The administration of small amounts of carcinogenic aromatic amines to individuals with aniline cancers of the bladder, and direct application of 3.4-benzpyrene to superficial cutaneous cancers was claimed by Bauer to have been followed by beneficial therapeutic effects. Such medication was, on the other hand, without any influence upon metastatic growths.

Similar contradictory evidence was reported concerning the action of these substances upon malignant cells. Appel, Strauss, Kolischer, and Necheles recorded that the injection of 1.2.5.6-dibenzanthracene into rabbits with Brown-Pearce carcinomas increased the growth rate and metastatic spread of these neoplasms, and raised the percentage of "takes". Lauber, Hildebrand, and Schocke found that the injection of small amounts of methylcholanthrene into carcinomas produced in mice with this chemical, sometimes resulted in the disappearance of the tumors, followed, however, by deep-seated sarcomas. Haddow and Robinson conceded that the alleged carcinocidal effect of carcinogenic hydrocarbons was more marked in transplanted Walker carcinomas of rats than in cancers produced by carcinogenic chemicals. Pybus and Miller stated that an intraperitoneal introduction of 1.2.5.6-dibenzanthracene was ineffective in influencing the growth rate of sarcomatous and leukemic conditions of mice. Creech (E. M. H.) tested carcinogenic and noncarcinogenic hydrocarbons in this respect and found that the carcinogenic compounds, 1.2.5.6-dibenzanthracene choleic acid, 20-methylcholanthrene choleic acid, and acenaphthene choleic acid, stimulate cellular proliferation and a precocious splitting of fibroblasts. The noncarcinogenic phenanthrene choleic acid and desoxycholeic acid cause a decrease of the growth rate. Toxic concentrations of carcinogenic hydrocarbons added to the culture medium retard cellular growth. Observations made in connection with the histological study of early develop-

mental phases of pulmonary cancers in mice and of bladder cancers in dogs, resulting from an exposure to aromatic carcinogenic substances, furnish additional evidence against the validity of the cytotoxic theory of chemical carcinogenesis. Experiences gained in this respect from occupational neoplasia point in the same direction, as a continued exposure to carcinogenic agents in the presence of an industrial malignancy is apt to accentuate the malignant and metastasizing qualities of a given cancer.

The reported inhibition of normal and neoplastic cellular growth is partly a chemo-toxic effect, and partly caused by direct trauma to the tumor tissue in those cases in which the carcinogenic material was introduced directly into the neoplasms. In conformity with common toxicological and pharmacological observations there does not exist a necessity or likelihood that the degree of toxicity of these chemical carcinogens is in any way directly related to their ability to induce malignant growths. In view of the numerous normal and pathological factors, which may cause an inhibition or a stimulaton of cellular proliferation without being related in any specific way with carcinogenesis, it becomes evident that the causation of malignant growths depends upon the action of agents which exert a more complex cellular or systemic effect than a direct inhibition or stimulation of cellular proliferation. The specificity of such a biological action is reflected by the observations made regarding the relationship of the chemical composition, structure, and configuration of various synthetic or industrially used carcinogenic and chemically related noncarcinogenic hydrocarbons, vitamins, hormones, sterols, and bile acids to their biological activity.

6. CELLULAR METABOLIC THEORIES

In the metabolic theories of cancerigenesis, various metabolic, cellular disturbances restricted to individual cells or groups of cells and elicited by abnormal environmental exogenous or endogenous influences are incriminated in the genesis of malignant growth (Warburg; Hammett; Reimann; Waldschmidt-Leitz; and Koegl).

Warburg advanced the theory that normal, growing cells exposed for a prolonged period to an interfered respiratory metabolism die or acquire malignant properties, by adapting themselves metabolically to such unfavorable oxidation conditions in order to obtain an appreciable part of the vitally needed energy from glycolysis not only under hypoxic circumstances, but also under aerobic conditions, and by transmitting this functional abnormality to successive generations of cells. This theory was based on the observation that a comparatively high, aerobic, glycolytic metabolism was found present by Warburg in a number of malignant tumors studied metabolically in tissue slices.

While this observation was confirmed by a considerable number of investigators, it was soon noted that there existed malignant tumors in which this

metabolic deviation was not pronounced or entirely absent. Apart from this lack of consistency it was found that a marked, aerobic, glycolytic activity was not specific for cancerous tissue. It was ascertained, upon more comprehensive investigation of the glycolytic activity of various normal and pathological tissues, that a more or less marked aerobic glycolysis was exhibited by embryonic tissue, cartilage, renal medulla, retina, and granulomatous tissue responses to virus and ordinary bacterial infections (Boyland; Dickens; Voegtlin; Druckrey; and Elliott and Baker).

Druckrey pointed out that an aerobic glycolysis is a phenomenon common to all injured cells, that the Warburg technique, using tissue slices, entailed a considerable and uncontrollable amount of cellular damage in the preparation of such slices, especially with soft and delicate cellular tissues, and that the degree of glycolysis determined by the Warburg method depended in part upon the amount of cellular injury present and, therefore, measured the metabolic activity of injured tumor cells. In contrast to the high anoxybiotic glycolysis of traumatized cancer cells noted by Warburg, Holtz found that healthy tumor cells possess a normal oxidative and glycolytic metabolism. Voegtlin, referring to the far-reaching conclusions of Warburg, stated that it would be more consistent with the well-established facts to regard the metabolic characteristics of tumors as secondary effects, which follow the transformation of normal cells into malignant ones and not as the cause of this transformation. A similar opinion on the obvious confusion of cause and effect in this respect was expressed by Rondoni.

Berenblum recently called attention to a mistake frequently made by supporters of the Warburg theory, who compare the metabolic activity of tumor tissue with that of some dissimilar normal tissue, such as slices of liver, kidney, or fibroblasts, normally possessing a metabolic activity differing from that of benign or malignant epidermal cells. When Berenblum measured the respiratory and glycolytic metabolism of normal epidermis of rabbits and epithelial tissue obtained from Shope's papilloma, very similar values were obtained for these two corresponding tissues.

Boyland and Boyland reported that the addition of 1.2.5.6-dibenzanthracene to the medium of slices of brain, spleen, and liver depressed the respiratory activity. On the other hand, Wiley observed that tissue slices from the liver and kidney of rats repeatedly injected with beta-naphthalyamine or kidney and liver tissue, surrounded by media containing this chemical in vitro, did not show any abnormal oxygen consumption or respiratory quotient.

Apart from the many contradictory results obtained from metabolic studies, clinical and morphological data indicate strongly that a prolonged interference with cellular respiration does not produce a favorable soil for malignancy. The relative rarity of cancer in chronically congested, cyanotic, fibrous, and atrophic tissues, such as cervices of completely prolapsed uteri (Leriche), chronic crural ulcers, and chronic hemorrhoids are striking demonstrations

of this fact. As histological data show that a well-vascularized, hyperemic tissue and not an ischemic, avascular tissue furnishes the basis of malignancy, occupational conditions characterized by anoxic, nutritive disturbances of a general or restricted type cannot be regarded as representing a suitable medium for an industrial malignancy.

Disturbances of the cellular or systemic sulfur metabolism were claimed by Hammett; Reimann; Grumme; Tanaka; and Sullivan to possess causal relations to the development of cancers. The most far-reaching contentions in this respect were made by Hammett. Elaborating upon his thesis that sulfhydryl, a natural constituent of all cells, is the essential and universal stimulus to growth by increase in the number of cells, and that the countless other auxenic factors exert their influence only indirectly through their effect on the sulfhydryl groups, Hammett proposed the following theory of cancerigenesis: The biological basis of malignant tumors is the distorsion of the sulfhydryl equilibrium in the presence of genetically determined lines of cells, in which the heightened nuclear reactivity of hypersensitivity to stimulation to proliferation by sulfhydryl, characteristic of young cells, is retained without resulting secondarily in increased differentiation. In support of this dogma, Hammett referred among others to the statement of Voegtlin and Thompson that tumor tissue contains glutathione in amounts comparable with those present in the liver, the organ having one of the greatest quantities of glutathione present in the various tissues. In a detailed review on the significance of sulfhydryl as a growth factor, Hueper showed conclusively that this theory was in direct disagreement with a number of well-established biological facts, was based on evidence of doubtful reliability, and was contradicted by data of numerous other investigators.

The available evidence scarcely sustains the fundamental claim made by Hammett and endorsed by Reimann, concerning the role of sulfhydryl as a universal and sole mitotic catalyst. This statement shall not distract from the significance which sulfhydryl compounds (methionine, cysteine, and glutathione) have as activators of certain enzymes, as oxidation-reduction regulators, as aminoacids essential for synthesis of protein and therefore for a sustained proliferation of cells, and as agents important in the detoxication processes of the body (Lightbody and Lewis; Mitchell and Hamilton; Hueper; Baker; Womack, Kemmerer and Rose; and White and Beach). Voegtlin, Johnson, and Thompson showed that a deficiency of sulfhydryl containing aminoacids in the diet resulted in a demonstrable impairment of the proliferative activity of normal as well as malignant cells, and that an identical result ensued from a dietary deficiency of other aminoacids, such as lysine. However, Hueper showed on explants of normal cells and Carr, Connor, and Ginzton on tumor-bearing animals, that the availability of excessive amounts of sulfhydryl in the nutritive medium has no effect upon the proliferative rate of cells after a certain optimum has been reached.

In an evaluation of these and additional data, Hueper pointed out that the available evidence indicated that sulfhydryl compounds do possess a protective function against the carcinogenic action of several well-known chemicals (arsenic, aniline, and tar) by operating as organic detoxicants (formation of conjugated ethereal sulfates and mercapturates) (Keeser; Young; Rosenthal and Voegtlin; and Thompson and Voegtlin). Following the outcome of later experiments Hammett as well as Reimann have repudiated their original contentions concerning the carcinogenic aspects of sulfhydryl, as Reimann and Hall could show that the skin of mice can be protected by the application of thiocresol against the cancerigenic action of 1.2.5.6-dibenzanthracene. These investigators concluded from this observation that a stimulation of the rate of cell division alone does not lead to neoplasia, and that carcinogenesis is the result of a damage to the potencies of differentiation and organization, which must be transmitted by a cell capable of division or by somatic mutation.

White and White recently furnished additional data on the protective effect of sulfhydryl compounds against the toxic action of two carcinogenic substances, methylcholanthrene and dimethylaminoazobenzol. They observed that the stunting of normal growth resulting in rats fed with these chemicals was prevented when the animals were placed on a diet containing adequate amounts of dl-methionine or l-cystine. It is thus conceivable that a deficiency of the body in sulfhydryl compounds, caused by a dietary deficiency of these substances or resulting from an excessive consumption of them in the body during the process of detoxication of exogenous chemicals, may favor the induction of cancer from external or internal carcinogenic agents (Grumme; and Sullivan). This aspect of the sulfur metabolism is obviously the important one from the standpoint of occupational neoplasia, and deserves much more attention and study for diagnostic, preventive, and therapeutic reasons than it has received heretofore.

Although Waldschmidt-Leitz and Voegtlin did not relate alleged abnormalities in the sulfhydryl content of malignant tissue to the induction of such growth manifestations, they maintained that such deviations are responsible for some of the most important biological characteristics of cancers, i.e., the infiltrative and destructive proliferation of malignant cells. In support of this claim the argument was advanced that, because of an excessive sulfhydryl content of cancerous tissue, there occurred an extraordinarily marked activation of the proteolytic enzyme, cathepsin, present in the cancer cells, which in turn were enabled to attack the surrounding normal cells and to spread in an invasive and destructive manner. It was contended that the proteolytic phase of the cathepsin activity was favored by the presence of an oxygen deficiency and an acid reaction, such as, resulting from excessive production of lactic acid of the malignant cells.

An adequate oxygenation and alkaline reaction, causing a shift in the intracellular equilibrium of sulfhydryl(-SH)-disulfide(-SS-) toward the oxidized

(-SS-)form, supposedly changes the proteolytic activity of the cathepsin-sulfhydryl combination into a proteosynthetic one (Voegtlin, Maver, and Johnson; and Rondoni), during which phase protein degradation products, formerly generated, are utilized as building stones in the construction of the cytoplasm of new tumor cells. The enzymatic studies of Waldschmidt-Leitz and his coworkers, however, could not be confirmed by Maschmann and Helmert; and Borger, Peters, and Kurz. Heinlein; and Morel and Delore were unable to substantiate the claim that necrotic tumor tissue contains an increased amount of sulfhydryl, thereby facilitating proteolytic processes.

Large cellular necroses, such as occurring in infarcts of normal tissue and in tumors, do not undergo a rapid lytic degradation, but are slowly resorbed and organized during the course of weeks or even months (Hueper). No reliable evidence exists supporting the claim that malignant cells can actively destroy normal cells with the aid of a special proteolytic process. Such a conception is fundamentally unsound, as infiltrative growth is by no means an exclusive property of "malignant" cells. It can be seen, sometimes, in a very striking form in connection with hyperplastic, epithelial proliferations in the edge of chronic ulcers or in endometrioses. In the latter it may give rise to heterotopic colonizations in distant organs, which are practically equivalents of metastases of malignant tumors. At any rate, a neoplastic growth stimulation following a traumatic production of necroses in tumor tissue cannot be attributed, with any degree of justification, to the release and presence of specific, growth, and proteolysis-stimulating sulfhydryl compounds.

While observations made in connection with the study of the synthetic, carcinogenic, aromatic hydrocarbons, and suggesting that abnormal transformations of the skeleton of the steroid substances of the body might possibly be the cause of many malignant growths (Cook and Kennaway; Dodds; Butenandt) have not yet led to conclusive results, Kögl and Exleben claimed recently to have furnished evidence indicating that the formation of cancer is causally related to the production of stereochemical deviations in the structure of the aminoacids composing the proteinic matter of malignant cells. These investigators claimed that the proteins of cancerous tissue consist not exclusively of l-aminoacids, the normal components of protein molecules, but in part of d-aminoacids, especially d-glutamic acid and d-lysin, thereby suggesting that tumor protein may be structurally isomeric to normal protein and differ in molecular size from the normal variety.

Interpreting these findings, Kögl contended that as the result of a stereochemical alteration of the cellular proteins cancer cells have lost the ability to utilize in the building of cell protein exclusively the natural l-amino acids, and that the presence of d-aminoacids in the cancer cells is responsible for the infiltrative growth of malignant cells, as normal cells did not possess suitable proteolytic enzymes for the hydrolysis of tumor protein consisting of d-aminoacids. As cancerigenic agents seem to attack the enzymatic protein syn-

thesis (Brock), Kögl connected this phenomenon with the autocatalytical production in vivo of an altered protease (cathepsin), which is generated in the tumor tissue endogenously in a fashion comparable to the exogenous development of tumor viruses. In further elaborating on the possible biological meaning of the alleged stereochemical protein abnormalities of tumor tissue, Kögl stated that the length of the latency period depended upon the rate at which d-aminoacids are incorporated into the cellular proteins. When the cellular contents of d-aminoacids surpasses a critical level, a fundamental change in the cellular character occurs, according to Kögl. The existing morphological differences between cancers of various types were attributed by Kögl to variations in the number and character of the d-aminoacids composing the protein matter of different neoplasms. Carcinomas were said to be distinguished from sarcomas by a higher content of d-aminoacids, providing a chemical substantiation of the different structural nature and biological behavior of these two types of malignant growths.

The chemical observations on tumor tissue made by Kögl were confirmed by Arnow and Opsahl; and White and White, but could not be substantiated by Chibnall, Rees, Tristram, Williams, and Boyland; Graff, Chargaff and Lipmann; Behrens, Kabat and Burk. The latter group of investigators pointed out that the uniformity and low order of d-aminoacids observed in a variety of hydrolysates examined, whether from benign or malignant tumors, normal tissues, or proteins, showed that malignancy is, as a rule, not specifically characterized by the presence of aminoacids of unnatural (d-) configuration. Klinke maintained, from his investigations on the d-aminoacid content of the rabbit myxoma, a virus propagated tumor, that d-aminoacids are not cancer specific in etiologic respects, but reflect merely local or general cellular or tissue disturbances.

While the contradictory character of the in vitro studies on the d-aminoacid content of cancers does not permit at the present time a definite decision concerning the validity of Kögl's claims from a chemical viewpoint, the speculative interpretations as to the biological significance of such stereochemical abnormalities, if actually existing, are unwarranted to a large extent by the evidence presented and are contrary to certain well-established facts. In connection with the theories of Waldschmidt-Leitz and Voegtlin it was mentioned that infiltrative and destructive growth is not a quality specific for and limited to malignant cells, as it is commonly observed with chronic, inflammatory, epithelial hyperplasias, endometrioses, and glioses, and can be reproduced in tissue cultures containing two types of tissue by varying the growth rate through changes produced in the environmental nutritive medium. Apart from this objection it must be doubted seriously that proteolytic enzymes are unable to hydrolyze tumor protein, as it is an every day experience to see cancerous necroses gradually absorbed by the invasion of the various phagocytic elements

of the organism. This indicates that the body is well able to cope with any unnatural proteins by the action of its normal cellular proteases.

It is, also, not permissible to draw any far reaching conclusions from the demonstration of quantitative differences in the d-aminoacid content of carcinomatous and sarcomatous tissues, as the distinction between these two types of malignant growths is to a large extent a purely morphological and therefore arbitrary one, and not a fundamental, biological one, based on consistent differences in the embryological or histogenetic origin of these tumors. Before any significance can be attached to the assumption that the morphological differences between various types of cancers are caused by specific differences in the number and character of the d-aminoacids present in the tumor proteins, it should be ascertained whether or not the corresponding differences in the morphology of the respective normal tissues are associated with similar variations in the chemical composition of the tissue proteins, which may be entirely unrelated to any d-aminoacid abnormality. Serious consideration should be given to the possibility that the observations of Kögl, even if proved correct, do not represent any primary changes possessing a causal importance, but are merely secondary cellular alterations occurring in cancer cells as the result of a cancerization. While mention has been made of the possibility of a d-aminoacid production in the process of cancerization in connection with the development of solar cancer (Jaeger), the evidence available at the present time does not support the claim that carcinogenic agents, particularly those of occupational type, induce a malignant transformation in cells by causing the enzymatic synthesis of unnatural d-aminoacids.

7. MUTATION THEORIES

It is obvious that whatever the mechanism is which brings about the changes in the activity and reactivity of normal cells transforming them into cancer cells, these alterations are of a fundamental nature, as the malignant cell is capable of propagating its own kind even in the absence of the original carcinogenic agent. Cancer cells may be regarded therefore as mutated cells. These mutations, their intracellular anlagen, or the predisposition to the development of such mutations may be inherited, congenital, or acquired, that is, genetic or somatic (Sutton; Luther; Teutschlaender; Bauer; Brock, Druckrey and Hamperl).

A. Inherited Mutation

It is theoretically possible that cancer cells may be formed in the embryonic organism on the basis of a genetic or chromosomal inheritance, and that such a direct cancerization may account for the occasional occurrence of malignant tumors in fetus or babies at or soon after birth. However, it appears more likely that even in such cases the cancerigenesis is the result of an interaction

of certain groups of cells, possessing a special inherited sensitivity to normal or pathological, endogenous agents endowed with carcinogenic properties, produced by the maternal or fetal organism and particularly active and present during the embryonic and fetal periods of life (Hintze). This conception is supported by the fact that malignant tumors showing hereditary relations of a dominant or recessive type observed in mice and appearing during the more advanced times of life depend for their induction upon the activity of additional endogenous and exogenous, extrachromosomal factors operating after birth (Fieser). Under such circumstances, the carcinogenic agents composing the intrinsic or extrinsic environment may not exert the same influence on all types of cancers possessing a hereditary factor.

The realization, that heredity plays a relatively limited and minor role in the genesis of malignant growths of man and animals, has developed rather recently. Before that time geneticists did not hesitate to assign to heredity an outstanding and dominating part in the production of cancers (Slye; Little; Lynch; Strong; Bragg; and Macklin). These claims were based on a long series of painstaking breeding experiments of mice, exhibiting apparently an inherited tendency to develop cancers of various organs (mammary gland, lung, and hematopoietic tissue). These findings were applied with comparatively little restrictions to man. The observations concerning a hereditary occurrence of cancers were made on so-called pure, inbred strains of mice, for which a high degree of homogeneity of their genetic, carcinogenic constitution was asserted.

Various considerations and facts, making their appearance during the last five years in an increasing number and force, have tended to greatly lessen the extent and significance of the original far-reaching claims. Strains of mice inbred for a large number of generations represent a biological material, which has no analogy in the human race and would be considered, if existing, as a highly pathological and undesirable breed. These pure strains of mice are for all practical purposes merely multiples of two parent individuals. These strains have been cleansed frequently by selective breeding of all those members exhibiting at any time genetic properties inimical to the desired cancerous predisposition. In spite of the prolonged efforts expended by various investigators to obtain genetically homogeneous strains of animals, most of the strains thus obtained showed only a limited homogeneity as to cancer heredity. Usually only a more or less considerable percentage of the animals belonging to such strains actually develop cancer during their normal lifespan.

These fundamental objections against the direct application of observations made in hereditary mouse cancerology were accentuated and widened in scope, when Bittner and Strong demonstrated the importance of extrachromosomal, environmental factors, such as the milk and dietary factors, upon the incidence of "spontaneous, inherited" mammary carcinomas of mice with known genetic constitution. Investigations of Andervont; and Lynch,

on the other hand, demonstrated that similarly marked alterations in the incidence of inherited pulmonary tumors in mice belonging to inbred strains could be produced with great ease by the cutaneous or subcutaneous application of carcinogenic agents, such as tar and various synthetic aromatic hydrocarbons. Andervont concluded from his evidence that there were only differences in degree of susceptibility among different strains, but not any variations in reactivity of any fundamental nature, as all strains tested with synthetic carcinogens reacted with pulmonary growths, when exposed to the carcinogenic agents to a sufficient degree. The experiments of Strong, showing the influence of various kinds of diet upon the mammary cancer rate, and those of Andervont; and Lynch demonstrating the effect of carcinogens upon the pulmonary tumor rate, are examples illustrating the importance of exogenous factors on the liability to cancer in the hereditarily conditioned individual. The experiments of Bittner, proving the carcinogenic significance of the "milk factor" contained in the milk and in various organs of predisposed animals, suggested the influence of factors of endogenous and, possibly of hormonal nature upon the susceptibility to "hereditary" malignancy.

These observations are of special importance for practical reasons, as geneticists have urged the use, for the testing of exogenous agents for carcinogenic potency, of animals with known genetic constitution. It is readily conceivable from the evidence presented that such a demand is ill considered. Although as Andervont; and Lynch have established the fact that marked differences exist in the reactivity of various inbred strains to the same carcinogenic agent, it is obvious that the use of one or even several of such strains renders only a limited amount of information concerning the potency of the agent under investigation, and may at times be greatly misleading as to the susceptibility of a species as a whole to a certain agent.

Large scale statistical studies on human material, made during recent years by Waaler; Macklin; and Martynova, and suggesting the presence and importance of hereditary factors in the susceptibility to cancer in man, are of very limited value because of the notorious inaccuracy of the human morbidity and mortality statistics. Macklin, in spite of these obvious and well-known limitations of the statistical evidence, insists that cancer is always due to an inherited factor and not to a mere predisposition, and that such an inherited factor accounts for the capacity of developing a specific type of tumor at a fairly definite time; while external factors only modify or aid the genetic factor by possibly hastening the time of onset. One must wonder about the disregard of the much more reliable contradictory evidence available in this respect, not only from experimental studies on animals, but also from an evaluation of the occupational neoplasia in man in regard to heredity (Barthélemy).

Borst pointed out that whereas the existence of a hereditary predisposition to cancer has been proven, the acquired predispositions and the exogenous

factors have a larger part in the ordinary human cancer than does heredity. Wood stated that the observations made in connection with the work on carcinogenic chemicals had resulted in a change in our notions as to the hereditary possibilities, and that it seemed probable that ultimately we may have to give up the idea of genetic relationships to cancer.

Bauer noted that only three neoplastic conditions in man can be traced to inherited factors (xeroderma pigmentosum, polyposis intestini, and neuroblastoma retinae). For all other tumors a monomeric inheritance can be excluded, in the opinion of this investigator, who does concede that hereditary factors may favor the action of exogenous, carcinogenic agents or endogenous, metabolic, or hormonal blastogenic disturbances. Crabtree called attention to the fact that an excessive, familial incidence of cancer does not necessarily imply the presence of a hereditary, genetic factor in the genesis of the disease, as common environmental agents may play a part in bringing about an excessive, familial cancer mortality. This applies especially to cancers of the skin, lip, and lung, while cancers of the female breast and internal sex organs are less likely dependent upon the action of environmental factors.

It may be possible that hereditary factors determine in a limited way the degree of susceptibility of different individuals to the various occupational, carcinogenic agents, and may account in part for the variations observed in the length of the exposure and latency periods. It is quite obvious, on the other hand, that practically all individuals will respond with a cancerous development to these agents when exposed to them sufficiently long and intensely. Any differences apparent in individual reactivity are not due to genetic factors, but to variations in the degree of exposure, and to endogenous and exogenous conditions influencing the degree of individual resistance (degree of pigmentations, sebum production, vascularization of skin in solar cancer, and availability of endogenous and exogenous detoxicants in chemical cancers).

The sum total of data available on the relationship of heredity to cancerigenesis indicates that the influence of heredity on this process remains, in general, in the same order in which hereditary factors act upon all other normal and pathological vital activities (Webster), such as metabolism and infections. There does not exist any more reason for exaggerating the role of heredity in regard to cancer, than there is for denying its part in modifying the reactivity and response of the body to the various extrinsic and intrinsic carcinogenic agents.

B. Congenital Mutation

In addition to an inherited susceptibility to cancer, there exists a nonhereditary congenital susceptibility. The neoplasias observed in twins, especially those of the homologous type, affecting often the same organ and appearing frequently at the same period of life, belong apparently to this type

of congenital cancerigenesis (McFarland and Meade; Roberts and Roberts; and Macklin). Such occurrences seem to be extremely rare, if the number of reported cases may be taken as a fair measure in this respect. The solar cancer of the skin developing on the basis of xeroderma pigmentosum, a congenital hypersensitivity to solar rays, is another representative of this variety of carcinogenesis, which includes probably some of the cases of intestinal malignancy originating from an intestinal polyposis of the childhood type.

C. Acquired Mutation

a. Direct Cellular Mutation

Both types of congenital suspectibility to cancer play only a minor and often only contributory role in the causation of cancers in general. The great majority of malignant neoplasms originate evidently on the basis of a cellular mutation acquired during life by the action of endogenous or exogenous, carcinogenic agents. Such specific cellular mutations may be brought about theoretically by two types of mechanism. The carcinogenic mutation may be the result of a direct cellulo-traumatic influence, such as exerted, for instance, by roentgen-rays and rays of radioactive substances, or it may be the outcome of an allergic sensitization to certain types of endogenous or exogenous factors, all of them probably of chemical nature. Although experimental investigations on various kinds of lower animals have demonstrated that the actinic agents are capable of producing cellular mutations, there exists very little, if any, direct or indirect evidence indicating that these agents produce by primary, cellular, physical traumatization mutations resulting in malignant growths. The claim concerning the occurrence of a direct, cytotoxic, chemical, malignant mutation of normal cells, which is mainly based upon the demonstration of chromosomic abnormalities in the number and morphology of these elements (Boveri), disregards the fact that identical chromosomic disturbances are produced by a great number of chemical agents, but never followed by the appearance of cancerous manifestations (von Möllendorf).

b. Allergic Mutation

The allergic theory of cancerigenic mutation is supported by a great number of observations relating to the morphological, hereditary, chemo-immunological, and other aspects of allergy. It, also, removes the process of cancerigenesis and continued malignant growth from its isolated position into which it is placed by other theories, and puts it among the many and varied, biological, cellular, and systemic reactions to pathogenic, exogenous and endogenous factors, particularly those associated with immune responses.

Allergy designates an abnormal state and reactivity of the organism and of the tissue at the site of contact with an antigenic agent to which the body has become hypersensitive, as the result of a previous exposure. The reactive phenomena observed in the tissue of contact, and the functional disturbances

noted in the organism remote from it are elicited by an antibody-antigen interaction (von Pirquet; and Opie.) Allergy is thus one of the phenomena connected with the production of biocatalytically active proteins (antibodies), which may differ from ordinary, inert proteins probably only by comparatively slight changes in the chemical arrangement and composition of the component aminoacids, and resemble enzymes in their functional reactivity in many respects. An analysis of the existing evidence reveals the following similarities and relations between allergic and neoplastic responses and phenomena.

Age. von Pirquet, who introduced the concept of allergy, claimed that the fluctuations in tumor incidence noted for the different age periods are related to variations in the allergic status of the organism. As the incidence of cancers in general increases with age, it is of importance that allergic diseases follow the same trend (Kämmerer). Many allergies develop after a prolonged but often discontinued exposure to the causative allergens, especially those of an industrial nature (Doerr), and thus show a long latency period similar to that present in occupational malignancies. Doerr as well as Kämmerer found that allergies are uncommon in babies, thereby displaying an additional similarity with the age distribution of malignant tumors.

Heredity. It has been stated previously that cancers are probably not directly inherited, but that only a special-tissue reactivity is transmitted, which may favor the development of a malignant tumor later on, if an exposure to a suitable exogenous or endogenous, carcinogenic agent is sustained. A similar concept is held in regard to allergies (Doerr). This investigator mentioned that only a certain predisposition to hypersensitivity diseases is inherited, while the type of allergy appearing in later life depends upon the type of exposure and on the nature of the allergen, which, in turn, control the character and site of the organ response (Hofmeier). Observations made in connection with occupational cancers (pitch and aromatic amines) and experimental pulmonary malignancies in mice (Andervont) have shown that, given a sufficiently heavy exposure to a carcinogenic agent, 100 per cent of the exposed individuals will react ultimately with a cancer regardless of the degree of heredity. Vaughan has made similar claims concerning the allergic responsiveness of man when subjected to similar conditions.

When Andervont concluded that the difference between inherently cancer susceptible strains and cancer refractory strains was merely a matter of degree, he expressed an opinion which is in perfect agreement with that of Lintz concerning the difference between normal, "nonallergic" people and allergic people in their response to gastrointestinal allergens. The occurrence of congenital allergy and malignant tumors in identical twins represents an additional similarity between these two reactions. A "congenital" but nongenetic sensitization in such cases may take place either by a diaplacental penetration of an allergen, or by a transfer of maternal allergens with the

milk (trophogenic hypersensitization) (Rosenau and Anderson; and Ratner). The observations of Bittner and Strong, concerning the role which the so-called "milk-factor" plays in determining the degree of susceptibility to mammary cancer in litters of mice, are possibly an example of such a mechanism of somatic sensitization. A direct absorption of such macromolecular allergens excreted with the milk through the intestinal mucosa of the newborn is made possible by the high permeability of this membrane during the early days of extrauterine life (von Möllendorf). The character of the allergen may account for the localization of the allergic-carcinogenic response in the mammary tissue.

Cancerization and Hypersensitization of Cells. Since none of the attempts so far made to cause a cancerization of isolated cells or cell groups of the same type (tissue cultures) by an exposure to carcinogenic agents of chemical and physical nature have been successful (Knake), it is significant that similar difficulties have been encountered in the production of allergic reactions in tissue cultures (Parker; and Salle and McOmie), when corresponding procedures were used. It is probable that the malignant transformation of cells and their hypersensitization represent primarily systemic and not purely cellular phenomena. After these changes have become established, the altered cells are capable of maintaining their abnormal character without the aid of any systemic influences, as both neoplastic and allergic tissues can be transplanted into non-neoplastic or non-allergic organisms, respectively, under preservation of their original properties (Schreus).

Morphology of Allergic and Precancerous Lesions. While the anatomical manifestations observed in allergic tissue reactions are still of controversial nature as to their specificity, there occur certain allergic lesions which display a definite similarity with those seen in pre-neoplastic responses. Nasal mucous polyps, which are in most instances of allergic genesis (Kern and Schenck; Semenov; Walsh and Lindsay; Hirsch; Hansel; Leroux and Delarue; and Weithe), show in their structure a striking similarity with the polypous growth observed by Hueper in the bladder of dye workers and dogs exposed to aromatic amines. There is in both cases a highly edematous, loose, and vascular connective tissue present forming the bulk of the polyp. Lymphocytes, leucocytes, plasma cells, monocytes, and eosinophilic cells occur in varying number in this matrix, and are located either in or around the lumina of the dilated vessels or form more or less diffuse or local infiltrations. The cellular elements of the matrix are sometimes inconspicuous, and there is a tendency toward a mucoid cystic degeneration. Beneath the surface of the nasal polyps glandular formations, sometimes of cystic character, are found.

The vesical polyps, on the other hand, may exhibit occasionally small epithelial cysts, characteristic of cystitis cystica. The epithelial lining of both types of polyps varies greatly in type and thickness with the individual case. The epithelial coat may be composed of a single layer of atrophic cells or

may be defective in places, leaving a bare surface. In other instances, there exists a thick, stratified, epithelial lining consisting of small, densely crowded cells, or of larger cells, which are of the columnar type in nasal polyps, but of the transitional cell type in vesical polyps. Metaplastic changes of a squamous cellular type occur especially often in nasal polyps, but rarely in their vesical counterparts. Papillary, hyperplastic, epithelial proliferations as well as malignant epithelial growths may occur in the bladder mucosa of man and dogs exposed to aromatic amines on the basis of such edematous polyps.

Attention may be called to vascular lesions observed in precancerous, polypous, and papillary vesical proliferations, as they provide additional circumstantial evidence suggesting the presence of an allergic developmental mechanism. The endothelial lining of the dilated precapillary vessels of these hyperplasias often show tiny, focal, endothelial proliferations projecting as small knobs into the lumina. In far advanced lesions of this type the vascular lumina are more or less completely obliterated by hyaline or fibrous endothelial thrombi, while the vascular walls are markedly thickened, fibrotic, and hyaline. Similar intima granulomas and alterations in the vascular walls are observed in allergic tissue reactions (Pagel; and Kuepper), and are regarded as the results of the fixation of an antigen or virus by endothelial cells. The precancerous vesical changes in man and dogs, exposed to aromatic amines and developing cancerous growths, resemble in many respects the histogenic allergic reactions described by Kolmer; Kline; Steinberg; Rössle; Aschoff; Doerr; Abrikosov; and Symeonidis.

Additional morphological evidence of an experimental nature supporting the conception of an interrelation between allergy and cancerigenesis was furnished by Reuterwall. He observed, after repeated and prolonged subcutaneous injection of egg albumin solutions into the ears of rabbits, the development of hyperkeratoses and papillomatosis, when an egg albumin solution was applied externally to the sensitized skin. Upon microscopic examination, the epidermis was found to be thickened and composed of swollen cells containing numerous mitoses, while the subepithelial connective tissue showed little evidence of an inflammatory reaction. Whereas there was no sign of a malignant cellular response, the allergic, hyperplastic, epithelial lesions closely resembled, in the opinion of Reuterwall, those seen during an early stage of cancerization of the skin following the injection of 1.2.5.6-dibenzanthracene in oil or of tar oil. Reuterwall suggested on the basis of these observations that cancer is the result of an allergic cellular mutation, elicited by a prolonged exposure to specific carcinogenic allergens and possibly continued, after establishment of the mutation, by a nonspecific, polyallergic stimulation furnished by chemically related endogenous or exogenous factors, which may replace the primary specific one (parallergy) (Stenn; and Rössle). Such a concept receives some indirect support from investigations of MacNider on the development of a nonspecific, cellular, metaplastic im-

munity of the tubular renal epithelium and of the liver cells of dogs, following the exposure to properly graded doses of certain renotoxic and hepatotoxic agents (uranium nitrate and chloroform). The chemo-immunity is characterized by the regenerative proliferation of cells which were not only morphologically and tinctorially distinct from the original normal cells of these organs, but also exhibited a higher resistance than the original renal or hepatic cells to the toxic effect of various chemical agents. They thus reveal a change in their reactivity, which is analogous to the so-called "hardening" observed frequently in industrial workers exposed to dermatotic allergic chemicals.

Nonspecific allergic reactivity of cancer tissue. Additional evidence pointing in the same direction is provided by the numerous observations on the effect of parenterally introduced foreign proteins into tumor-bearing animals and man. Injections of certain types of foreign protein, especially those of bacterial origin, elicit in the tumor an acute inflammatory and necrotizing response characterized by edema, hemorrhage, degenerative changes in the tumor cells, and necrosis, resulting in temporary regression and arrest of tumor growth, and in some experiments frequently in permanent cure. The changes noted have a marked similarity with those present in the Shwartzman phenomenon (Abrikosov).

Reactions of this type were apparently first observed by Fehleisen, who reported permanent cures in two cases of human cancer following the therapeutic infection with erysipelas streptococci. Spronck, using sterile filtrates of these bacteria for a similar purpose, observed in some of the 7 dogs with spontaneous tumors and 25 patients with inoperable neoplasms thus treated degenerative changes in the tumors accompanied by inflammation and hemorrhage which he attributed to the capillary dilatation and serous exudation locally in the tumor, caused by the bacterial toxins introduced. A selective degenerative effect of bacterial substances, such as sterile preparations of erysipelas streptococci and B. prodigiosus, upon tumor tissue, especially bone sarcomas, was also reported by Coley, and has been utilized by him for therapeutic purposes in a large number of cases with curative results in an appreciable percentage. The temporary regression seen in tumors after the parenteral introduction of milk and similar substances may belong to this group of reactions (Petersen).

Similar selective hemorrhagic necroses can be produced in transplanted tumors by the parenteral introduction of certain bacterial factors, which are capable of producing local skin reactivity (Shwartzman phenomenon). Transplanted tumor tissues behave in this respect like transplanted allergic tissue, which retains its hypersensitive reactivity (Kolmer).

The first experiments suggesting this type of reaction were performed by Beebe and Tracy. They observed in dogs, inoculated with a transplantable lymphosarcoma, a softening of the tumors with accumulation of fluid. This

was followed by regression and sometimes by complete disappearance of the new growths after the injection of sterile cultures and filtrates of B. coli communis, staphylococcus communis aureus, streptococcus pyogenes, and B. prodigiosus. Intratumoral hemorrhage and liquefaction of a transplantable liposarcoma in guinea pigs subsequent to the injection of filtrates of B. coli cultures were reported by Gratia and Linz. Similar observations were made by Shwartzman; and Shwartzman and Michailowsky working with tumor-bearing mice (sarcoma 180), after the intravenous injection of killed cultures and filtrates of meningococci, B. enteritidis, and B. typhosus. In one of these experiments Shwartzman recorded prompt hemorrhagic necrosis and regression of the tumors in 2 out of a total of 27 animals used, followed by an uneventful permanent healing in 21. This is a remarkable result in view of the fact that spontaneous regressions with permanent cures are rarely observed in tumor-bearing mice (about 1.33 per cent according to Woglom). These results and observations were subsequently confirmed by Shear in similarly conducted experiments.

A further contribution to this subject was furnished by Apitz, who injected mice with Ehrlich carcinomas with cultures of B. coli and observed hemorrhagic and necrotic changes entirely restricted to the tumor tissue in these animals. Duran-Reynals, using rats and mice with transplanted tumors and employing filtrates of B. coli, stated that rapidly growing tumors are very susceptible to the blood-carried toxin of B. coli; while slow-growing, malignant, spontaneous and transplanted tumors; malignant tumors rapidly growing in heterologous hosts; embryomas; and granulomas are practically non-susceptible. He also found, in agreement with observations made by Apitz and Shear, that young tumors are usually not affected. This may possibly be attributed to the fact that, owing to the existence of insufficient vascular connections of the tumor tissue with the tissues of the host at such time, reacting substances introduced into the blood of the host may not reach the tumor tissue in appropriate quantities. It is also conceivable, that for the same reason and on account of the presence of only small necroses in the inoculated piece of tumor tissue from which specific substances can be released, sensitizing agents have not yet entered the host organism in sufficient quantities to set up an immunity reaction.

Gratia and Linz; and Apitz, who made a pathologic study of tumors thus treated, observed that the hemorrhagic zone lies between the necrotic central portions of the tumors and the peripheral area of most recent tumor growth. Apitz reported that the histologic examination of such tumors showed the presence of markedly dilated and hyperemic blood vessels, often but not always associated with high grade edema and hemorrhages in the tumor tissue, caused by dieresis of the vascular wall, resembling in character those seen in the Shwartzman phenomenon. In addition to the hemorrhagic imhibition of part of the tumor tissue resulting in secondary parenchymatous nec-

roses, there were apparently primary degenerative changes of the tumor cells present, which were independent of the hemorrhagic effect and also occurred in the absence of hemorrhages. The cancer cells were hydropic and showed vacuolization. Apitz concluded that these local, nonspecific *hyperergic*, intratumoral reactions, which can only be elicited by Shwartzman active substances, cause, in addition to primary circulatory disturbances restricted to the tumor area, primary parenchymatous regressive changes in the tumor.

Duran-Reynals attributed the intratumoral vascular reaction, which has also, according to him, the general characteristics of the Shwartzman phenomenon, to two sets of factors: an intrinsic one, depending upon the sensitivity of the tumor itself; and an extrinsic one, depending on the activity and quantity of the bacterial toxin administered. He believes that the newly formed vessels of a malignant tumor, either as a consequence of excessive permeability or some other cause, are peculiarly sensitive to blood carried bacterial toxins, and that this vulnerability is responsible for the regression of the tumor. These observations were confirmed by Rogg as well as Jacobi, who obtained by similar procedures similar intratumoral, necrotizing and hemorrhagic reactions not only in tumors of mice (sarcoma 180), rats (Flexner-Jobling carcinoma and Walker carcinosarcoma 256), and chickens (Rous sarcoma) sensitized to various bacteria (B. typhosus and B. proteus), but also in a breast carcinoma of a woman complicated by axillary metastases. The results of these investigations suggest that cancer tissue behaves like or is an allergic tissue.

Chemo-Immunological Relations

The evidence presented thus far concerning the possibility of allergic-carcinogenic interrelations is obviously more or less circumstantial and open to criticism. Similar objections may be raised against the statement of Bernstein, that all the facts supplied by a statistical analysis of the experimental data obtained from Lynch; the Crocker Institute; and Loeb and Lathrop are consistent with the conception that cancer is an allergic disease. Boyland and Warren claimed from the results of a statistical evaluation of neoplastic responses obtained in mice, following the injection of single and repeated doses of methylcholanthrene, that the carcinogenesis is of the nature of a drug reaction and that it is improbable that carcinogenesis is an allergic reaction. Martin suggested the possibility of an allergic genesis of rectal carcinomas, while Grynkraut proposed a corresponding causal mechanism for the development of actinic cancers.

It is fortunate, therefore, that the proper correlation of some immunologic and clinical observations made with certain organic compounds, which have allergic and carcinogenic qualities and have been extensively produced and used for commercial and medicinal purposes, seems to supply a few of the missing links needed for strengthening the above concept.

Among the large number of compounds included in the group of aromatic amines and their derivatives, there are substances with more or less marked allergic properties, which are responsible for the frequent appearance of dermatitis, asthma, and rhinitis among persons coming in contact with them (phenylene diamines, para-amino-phenol, aurantia, and phenylhydrazines). Also, there are compounds which combine with allergic qualities those of cellular growth stimulation, sometimes leading to tumor formation (aniline, benzidine, naphthylamine, toluidine, chrysoidine, Bismarck brown, and amidoazo-toluol) (Koelsch; Mayer; Sulzberger; White; and Sachs). Teutschlaender; Mayer; Kimla; Bettazzi; and Beck called attention to the allergic nature of tar dermatoses and tar cancers, respectively. Similar combinations of allergic and carcinogenic qualities exist in certain, inorganic, blastogenic agents, such as nickel, arsenic, and chromates.

Definite proof of the allergic nature of carcinogenesis depends upon the demonstration of chemospecific, carcinogenic allergens by chemical and immunological methods, and of an effective prevention of carcinogenesis in a sensitized organism by means of a specific desensitization. Mayer; Hueper; Needham; and Oesterlin have advanced the conception that the carcinogenic action of various synthetic and occupational, carcinogenic chemicals depends upon their ability to couple either directly or as metabolites with protein molecules in the body, thus forming allergenic, hydrocarbon-protein complexes.

While the isolation of such chemospecific, carcinogenic hydrocarbon (hapten)-protein complexes from cancerous tissue has not been accomplished as yet, there exist a large number of observations in which such conjugations have been obtained in vitro with relatively simple chemical means. The resulting allergenic products (immune sera) showed a high degree of chemospecificity in the haptenic group in immunological reactions, and exerted, under proper experimental conditions, when tested in animals, an anticancerous effect.

There exist various methods by which aromatic substances, especially aromatic amines, may be coupled with proteins. The oldest and most often used technique is that leading to the production of the so-called azo-proteins. It was discovered by Pauly and later on elaborated and applied to the chemo-immunological field by Landsteiner. The following procedure is used: aromatic amines are diazotized by the addition of sodium nitrite and hydrochloric acid, and the resulting diazo-compound is conjugated with certain aminoacids (histidine and tyrosine) of the protein molecule. If the diazo-compound is present in excess it may also combine with the indole group of tryptophane, the imino-group of proline and oxyproline, the imidazo-group of histidine, or with free amino-groups of any aminoacid present. The azoproteins obtained have the general structure $R—N{=}N—C_6H_5$. Such azoproteins have been formed with aniline, benzidine, beta-naphthylamine, alpha-naphthylamine, toluidine, beta-anthramine, amidoantipyrine, p-aminophenylazobenzene, p-aminobenzophenone, p-aminophenylmethane, and atoxyl (Landsteiner and

Lampl; Landsteiner and Jacobs; Landsteiner; Jacobs; Breinl and Haurowitz; Heidelberger and Kendall; Erlenmeyer and Berger; Berger and Erlenmeyer; Eagle and Vickers; Mutsaars and Grégoire; Marrack; and Klopstock and Selter).

Animals injected with these azoproteins developed immune bodies (precipitins and complement fixing antibodies) against the particular haptenic group and chemically related substances (group-immunity). Erlenmeyer and Berger reported that an immune serum against an amino-antipyrin-protein complex reacted with aniline, acetylphenylhydrazine, histamine, histidine, and those pyrazolon compounds containing the $C_6H_5—N=N—C—H_3$ group, which is responsible for the antipyretic effect displayed by aminoantipyrine. An antiserum against the diazo-compound of beta-aminopyridine yielded positive immune reactions with beta-aminopyridine, pyridine, alpha-picolin, beta-picolin, collidin, nicotinic acid, coramine, quinoline, and nicotine. Jacobs found that antisera against the azoproteins of aniline and toluidine did not interact with polycyclic hydrocarbons, such as diphenyls, naphthylamines, and anthramines, while naphthylamine antisera reacted with various polycyclic antigens. These group immune reactions are of importance not only from the viewpoint of providing an explanation for the well-known observation of polyallergy, but also from the consideration that a noncarcinogenic hydrocarbon may elicit an allergic status to a chemically related, carcinogenic substance and vice versa.

The second method by which proteins can be conjugated with aromatic compounds was developed by Hopkins and Wormall in 1934. These investigators used the phenyl-isocyanate method for producing with the ureido-linkage ($R—\underset{\underset{O}{\|}}{C}—NHC_6H_5$) allergenic, hydrocarbon-protein complexes. In the production of these compounds, the aromatic isocyanates react mainly with the epsilon amino-group of the lysine molecules and occasionally with the tyrosine molecule of the proteins, forming carbamidoacids. This technique has been employed extensively by Creech and Franks; and Fieser and Creech for the coupling of various carcinogenic hydrocarbons and numerous, non-carcinogenic, cyclic compounds with proteins in their investigation of the immunizing properties exerted by these complexes against hydrocarbon carcinogenesis.

These allergens are of special interest in connection with the occupational cancer problem, as they suggest a possible route by which water insoluble carcinogens may be converted into water soluble ones, and because of Boyland and Levi's observation concerning the excretion of certain polynuclear aromatic hydrocarbons fed to animals, in part, in conjugation with aminoacids (Fieser and Creech). A possible interaction of aminoacids with carcinogenic hydrocarbons in the organism seems more likely by the experiments of White and White, who found that sulfhydryl containing aminoacids counteract the growth inhibiting action of toxic doses of carcinogenic hydrocarbons upon young animals.

It is of significance from an allergic view-point that ureido-antigens give

cross precipitin reactions with azosera, and azoproteins interact with ureido sera (Mutsaars and Grégoire). Consequently, the number of possible group reactions is definitely enlarged together with the scope of polyallergy.

A third method of conjugation of proteins with aromatic hydrocarbons was described by Gaunt, Higgins, and Wormall in 1936. These investigators coupled at a neutral reaction proteins with a benzyl carbonyl chloride, forming a benzyl carbonato-protein ($R–HCHN \cdot OCOH_2CH_5C_6$). This allergenic protein complex possesses a reduced number of free amino groups and an intact protein specificity, which is destroyed in the course of the preparation of the above-mentioned protein conjugates. This method represents an elaboration of a technique used in 1933 by Bergmann and Zervas in the conjugation of benzylcarbonyl chloride with aminoacids. The injection of the benzylcarbonato-proteins gives rise to the development of precipitins and complement fixing immune bodies.

Wood and Fieser suggested recently that a carcinogenic hydrocarbon may combine directly with an intact constituent of the cell protoplasm by becoming attached to one sulfur following the opening of the proteinoid disulfide (-SS-) linkage. This interaction between carcinogen and cellular protein may represent the initiating change leading to carcinogenesis.

Azophenol glycosides of glucose and galactose coupled with globulin, such as p-aminobenzyl-beta-glucosides of glucose or glucuronic acid, possess an antigenic character, and cause the production of chemospecific antibodies (Goebel, Avery, and Babers; and Goebel and Goodner). Bergmann and Fraenkel-Conrat obtained in vitro by the action of papain, combinations of aniline with acetyl-, benzoyl-, and carbobenzoxy-derivatives of alanine, leucine, and phenylalanine. Only the laevo-forms and not the dextro-rotary isomeric aminoacids participated in these reactions.

In addition to the sensitizations produced in animals by the introduction of aromatic hydrocarbon-protein complexes, there exist a number of experimental observations, confirming similar clinical evidence, which indicate that certain non-conjugated, aromatic chemicals may elicit allergic reactions when brought in contact with the tissues of man and animals [arsphenamine (Swift); neoarsphenamine (Frei; and Sulzberger); phenylhydrazine (Jadassohn); p-phenylene diamine (Mayer; and Diener); 2.4-dinitrochlorobenzol, 1.2.4-trinitrobenzol, p-cresylchloride, and various dichlorodinitrobenzols (Landsteiner and Jacobs); p-aminophenol, p-nitrosophenol, 2.4-dinitrophenol, and acetylaminophenol].

Other chemically similar substances, tested by the same method gave negative results in the hands of Landsteiner and Jacobs (nitrochlorobenzols, quinine, resorcine, acetylsalicylic acid, dibenzanthracene, and diazo dyes coupled with resorcinol), in spite of the fact that some of these substances have given rise to drug allergies in man. Subcutaneous, intravenous, or intraperitoneal injections of suspensions of 1.2.5.6-dibenzanthracene, 3.4-benzpyrene,

and 3.4.5.6-dibenzcarbazole in serum (Boyland and Warren), as well as of solutions of beta-naphthylamine in acidulated water and serum, respectively (Hueper, Briggs, and Wolfe), into rabbits, dogs, and rats did not result in the production of antibodies demonstrable by serological methods, anaphylaxis tests, or passive skin sensitization. These observations indicate that the chemicals used must be conjugated with proteins before immune reactions can ensue.

There exists a certain amount of chemical and immunological evidence showing that quinones and quinogenic aromatic substances may combine directly with proteins (Suida; Landsteiner; Mayer; and Gerdon). This reactivity of quinones accounts for the dyeing properties of animal fibers displayed by various azodyes, and for the yellow color exhibited by nitro- and azo-proteins. It is probably the reason for the tendency of the quinogenic paraphenylene diamine and its derivatives to elicit various kinds of allergic reactions (asthma, rhinitis, and dermatosis) in chemical workers and furriers. The quinone bodies react with the aliphatic amino-groups and sulfhydryl groups of the amino-acids, forming dark-colored polymerization products.

Sometimes only minor changes in the molecular structure of the aromatic compounds may result in marked shifts in their readiness to couple with proteins, in the type of protein complexes formed, and in the specificity of antibodies produced (Oesterlin; and Marrack). Marrack stated that the shape and size of a particular molecule influence the physico-chemical properties of these large and complicated molecular complexes, and that, because of this, the location of the atoms, the type and character of the side chains, their sizes, grouping, and configuration determine the chemo-immunological reactivity, and explain the existence of steric hindrance in the production of group reactions, as bulky side chains or closely adjacent side chains may cause distortions of the molecule. Such molecular alterations are important in immunity reactions, as intermolecular adsorptive phenomena play a decisive role in such processes. The intermolecular adsorption depends, in turn, upon the character of the polar forces or secondary valencies, which determine the possibility of group reactions (Marrack), that are an expression of the specificity of the binding of polar forces. Minor deviations in the spatial arrangement of identical side chains of cyclic compounds may cause fundamental differences in their adsorbability. This applies even to optical isomers, as levo- and dextro-rotary forms differ in their distribution of the polar fields.

On the other hand, immunological tests have shown that several determinant groups may have equivalence. Thus a benzene ring may be replaced in a compound by a thiophene ring, a naphthalene ring, a cyclohexane ring, or compounds with a CH_2 group, O group, or NH group in a side chain may form equivalent antibodies. This phenomenon may be explained, according to Marrack: 1. by the presence of atoms or groups of atoms of appropriate fields of force in the determinant group of the antigen, and in the receptor sites of

the antibody; 2. by a proper spatial distribution such that corresponding active points of antigen and antibody can come in apposition simultaneously; and 3. by the accessibility of the active points of the determinant groups to the antibody, owing to the absence of any large inactive group that would prevent or obstruct this approach. The introduction of polar groups into the less active parts of the determinant group affects the specificity of the immunological adsorption on account of 1. differences of electronic distribution; 2. differences in location of polar groups not fitting into receptors; and 3. production of spatial obstruction preventing combination with antibody (Marrack).

It is of significance and in support of the validity of the allergenic theory of cancerigenesis that similar chemical and stereo-chemical interrelations (composition, configuration, spatial arrangement, and size of side chains) seem to possess a decisive influence in determining the carcinogenic potency of the aromatic hydrocarbons (Bradley), as they are noted in connection with the chemo-immunity reactions of these and chemically related compounds. Investigations with various benzanthracene derivatives showed that compounds with substitutions in the 10., 9., 6., and 5. positions possess carcinogenic properties as long as the side chains are relatively short, while these specific qualities are greatly diminished or entirely absent in benzanthracene derivatives with substitutions in other positions (Cook and Kennaway). A similar reducing effect upon the carcinogenic potency of these compounds is elicited by too great an elaboration of an effective type of structure (Fieser, Fieser, Hershberg, Newman, Seligman and Shear; Kennaway; and Barry, Cook, Haslewood, Hewett, Hieger, and Kennaway).

In some of these hydrocarbons, such as methylcholanthrene, the molecule can be stripped of certain of its appendages without the loss of its carcinogenic potency. Similarly, one of the angular rings of 1.2.5.6-dibenzanthracene can be replaced by a cyclopenteno ring or by two methyl groups, respectively, with retention of the original potency (Fieser). The importance of stereochemical factors in determining the carcinogenic properties of these compounds is illustrated by the fact, that various heterocyclic isologues of the higher aromatic hydrocarbons (1.2.5.6-dibenzacridine and 3.4.5.6-dibenzacridine) are only feebly carcinogenic (Fieser), while the structural isomers of o-aminoazotoluol are not hepatocarcinogenic at all (Shear; and Kinosita). The influence of the character of the substituting groups upon the carcinogenic potency of these cyclic hydrocarbons is exemplified by the fact that the introduction of a hydroxy-group into the 3.4-benzpyrene molecule and into the methylcholanthrene molecule, respectively, destroys the carcinogenic quality of these compounds; but the substitution of a hydroxy-group for an amino-group in aminoazotoluol results in the loss of the carcinogenic organ specificity of this compound, which is shifted from the liver to the bladder (Nagao; and Kinosita).

The position of the substituting groups exerts an influence upon the relative

degree of carcinogenic potency of closely related compounds. Thus, benzanthracene derivatives with substitutions in the 5.6. positions are most active. A substitution in the 10. position increases the potency as much as one in the 6. position (Bachmann, Cook, Dansi, DeWorms, Haslewood, Hewett, and Robinson). While it is not known if carcinogenic hydrocarbons are carcinogenic in their original form or acquire this property as the result of some metabolic transformation, such as oxidation or reduction, and while all active carcinogenic compounds are extremely susceptible to the action of oxidizing agents, Fieser pointed out that the first products of their chemical oxidation and reduction, show diminished, rather than enhanced, activity. Fieser was disinclined to concur with the suspicion of Barry, Cook, Haslewood, Hewett, Hieger, and Kennaway, that the role of the carcinogenic substances may be associated with some interference with the normal oxidative processes of the cells; and was reluctant to accept the dogma of Hammett, that the carcinogenic substances act through an influence upon the reducing processes of the cells.

These chemical observations receive a more definite meaning since Creech and Franks could show that immune sera, produced in rabbits by the injection of anthranyl-carbamido-protein and 1.2.5.6-dibenzanthranyl-carbamido-protein, convey a certain degree of anticancerous immunity upon mice treated with the corresponding carcinogenic haptens. There was some evidence indicating that these immune sera elicited a cross-immunity against a carcinogenesis by methyl cholanthrene. These investigators concluded that a serological immunization by such a procedure should lead to protection against endogenous and exogenous carcinogens.

Such a conclusion is compatible not only with the present knowledge in regard to chemo-immunity (chemo-allergy, polyallergy, and latent allergy), but is also in accord with the recent demonstration of antihormones. It is of special significance that the repeated injection of gonadotropic hormones, which are chemically closely related to certain synthetic, carcinogenic chemicals and various sterols and bile acids normally occurring or entering the body, resulted in chemospecific antihormones, according to clinical and experimental observations (Collip; Collip, Selye, and Williamson; Severinghaus and Thompson; Gordon, Kleinberg, and Charipper; Fluhmann; Kindermann and Eichbaum; Bauer; Ehrlich; Bachmann; Brandt and Goldhammer; and Twombly). The antihormonal inhibins produced did not prove to be strictly specific, but gave serological immune reactions with chemically related substances (Bauer). It remains to be seen whether or not the inhibiting action exerted by large doses of androgen and testosterone propionate, respectively, upon the development of methylcholanthrene cancers and benzpyrene tumors in mice can be attributed to a chemo-immunological influence of an antiendocrine immunity upon a malignant process (Flaks and Ber).

One must consider that sterols (cholesterol, ergosterol, and derivatives) can be endowed with antigenic properties and may give rise to chemospecific

antibodies (Sachs and Klopstock; Berger and Scholer; Wadsworth, Maltaner, and Moltaner; Štefl; and Weil and Besser). It is of significance that not all sterols display such qualities, according to Weil and Besser. Cholesterol dibromide, cholesterol acetate, cholesterol oxide, and cholesterol palmitate do not possess any antigenic qualities. As the presence or absence of antigenic potencies in cholesterol derivatives is found to be related to changes in the substituting groups, the high and decisive importance of the character of the side chains in regard to the biological action of polycyclic hydrocarbons receives renewed emphasis.

The normal and pathological processes to which the organism is subjected afford ample opportunity for a synergistic or potentiated action of antigens which, while not carcinogenic by themselves, may possibly continuate or accentuate a carcinogenic-allergic reaction elicited by specific, but chemically related exogenous or endogenous agents. The occurrence of such interactions seems to be the more readily conceivable, as Landsteiner and van der Scheer showed that, after the establishment of a chemospecific immunity to aromatic substances, the hapten alone is sufficient to elicit immune reactions. Apart from a possible activation of carcinogenic, allergic reactions by noncarcinogenic agents, there exists the possibility of a direct stimulation by exogenous substances displaying a dual activity, the carcinogenic phase of which may not always be suspected.

Browning found that styrylquinoline possesses trypanocidal properties and cancerigenic ones. Aschheim and Hohlweg reported that some extracts from bituminous material, such as coal and mineral oil, exhibit estrogenic qualities (Loeb), which are probably attributable to the presence of carcinogenic substances, as 3.4-benzpyrene and 5.6-cyclopenteno-1.2-benzanthracene are capable of eliciting in mice a full estrous response. The possibility of the existence of similar interrelations in regard to ergosterol derivatives is suggested by the fact, that some of these substances (calciferol and neo-ergosterol) affect the calcium metabolism, and also possess estrogenic properties (Störmer and Westphal; Marrian; and Dodds). The postulated occurrence of carcinogenic qualities in these sterols, in addition to that of the estrogenic and hypercalcemic ones would depend on the presence of special chemical groups in their molecules, as estrogenicity is conveyed by chemical groups which are not identical with those causing carcinogenicity.

While the allergic concept of cancerigenesis remains at the present time within the realm of theory, it is believed that the evidence presented furnishes sufficient support for the claim that this theory is more compatible with the existing facts, providing a general denominator for them, than any other theory so far proposed. No other theory, with the possible exception of the virus theory of cancerigenesis, can furnish a plausible explanation of the mechanism active in the production of malignant occupational neoplasms, appearing many years after the cessation of exposure to the cancerous noxae.

It is readily conceivable that a cancerigenic allergic reaction may remain dormant or in a sub-manifestation stage for a number of years, until either a nonspecific realization factor or the action of nonspecific, polyallergic agents, possibly represented by cyclic aminoacids, such as indol, skatol, and tryptophane, which promote cellular proliferation and hasten tumor production by benzpyrene (Cook and Kennaway), cause the ultimate activation of the allergic tissue into a cancerous growth. Similar considerations apply to the not infrequent delayed appearance of metastases many years after the surgical or roentgenological eradication of the primary tumor. It is obvious that some unknown forces must keep such cancerous foci in a nonproliferative state over prolonged periods and that changes in this environmental status bring about an activation. Fluctuations in the immunity conditions to certain infectious diseases are accompanied by similar activations.

D. Virus Cancerigenesis

As various avian cancers (Rous sarcomas) and several mammalian blastomatoid and blastomatous manifestations, such as common warts in man, infectious papillomas of dogs and cattle, and the papillomas of the cotton tail rabbit, are caused by a filtrable virus, attempts have been made to extend the virus etiology to cancers in general (Rous; Andrewes; Stanley; and Besredka). The last mentioned investigator proposed the hypothesis that a neoplasm is a defense reaction against a tumor-forming virus, which appears to be widespread in distribution and which is unable to act, unless there is a localized weakening in the natural immunity of the tissues.

Andrewes stated the case of the virus theory of carcinogenesis as follows: "This theory postulates the existence of a virus or viruses, widely distributed in the animal kingdom; that they are latent infections, but are lit up by some stimulus such as the application of a carcinogenic hydrocarbon."

Rivers noted that "it is an acknowledged fact that some tumors are caused by viruses, at least, most investigators will admit that some viruses produce hyperplastic growths with all the immediate traits of tumors. Indeed, hyperplasia and necrosis are such important phenomena in the pathological pictures induced by viruses that pertinent remarks had to be made concerning tumors, if for no other reason than to emphasize the fact that such disease processes as tumors, warts, measles, fever blisters, smallpox, varicella, poliomyelitis, rabies, yellow fever, fowlpox, foot and mouth disease, tobacco mosaic, and bacteriophagy, in spite of their striking clinical differences, possess in common characteristic pathological pictures."

Rous, confronted with the difficulties that stand in the way of the supposition that cancers in general are due to viruses, advanced the following arguments: 1. The cause of cancer must be present wherever man is. But wherever he goes so do certain of his parasites. May he not take viruses as well? 2. The sporadic occurrence of cancer attests the lack of infectiousness. The natural

incidence of chicken tumors yields no sign whatever that they are caused by a virus. Their occurrence is highly conditioned and some of them obviously represent a triumph over resistance offered by the host. 3. In the failure of attempts to demonstrate an extrinsic cause for the generality of malignant mammalian tumors, technical difficulties may have been mistaken for a biologic principle. 4. The appearance of malignant tumors of the same sort in identical twins, or in hereditary glioma of the retina, and in von Recklinghausen's disease may mean no more than, when the soil and contributory circumstances are right, a carcinogenic agent, perhaps a virus, is effective as it would not otherwise be. 5. The experimental induction of cancer at sites where it never occurs normally indicates that some decisive condition or agent is evidently present in the areas at which they arise. Andrewes has given reasons for supposing this agent was a virus entering the organism previously and ensconced in the epithelium at the time when the carcinogenic substance was applied—an indigenous virus, as he terms it. 6. Cancer does not spring full blown from normal cells, but develops as the result of gradual and often long continued changes. The changes induced by all the various carcinogenic agents may be of a sort to urge a symbiotic virus or viruses to pathogenic activity. 7. Metastases of several differing sorts, representative of more than one germ layer, are occasionally encountered in patients dying of a teratoma that becomes malignant. Many teratomas are supposedly derived from pluripotential sex cells and, if one of these became infected with a tumor-producing virus, secondary growths of diverse character would occur as a matter of course. 8. Since viruses are highly specific in their action, one causing osteochondrosarcomas of the fowl, for example, another endotheliomas only, an entire microcosm of viruses would be needed to account for all the malignant tumors.

Andrewes suggested that the milk factor of Bittner is not a hormone secreted into the milk and ingested by the baby mice, because the effect of this milk factor is demonstrable in the second generation of mice thus exposed, and a biological action of an orally introduced hormone is improbable. Andrewes proposed that the milk factor represents an infection of the young mice with an indigenous virus, the habitat of which is the milk through which it is transmitted. This conception has been endorsed recently by Bittner, in view of the results obtained in mice following the feeding of lyophilized tissue prepared from breast tumors.

Numerous attempts have been made to establish a relationship between cancers caused by chemical agents of occupational significance (tar and carcinogenic polycyclic hydrocarbons) and virus infections. Since the original, carcinogenic, exogenous factor of such neoplasms disappears completely from the tumor tissue after a few transplantations and cannot be demonstrated in metastases (Lorenz and Shear), an attempt was made to isolate from such blastomas a filtrable virus or virus-like protein complexes, or to make the presence of such an agent probable by immunological reactions.

McIntosh obtained in 1933 four tumors in fowls treated with tar, three of which could be propagated readily by filtrates prepared from the original neoplasms. Sarcomas produced in chickens by the injection of tar or 1.2.5.6-dibenzanthracene proved to be of the non-filtrable type (Sturm and Murphy (1928); Peacock (1933); Mellanby (1934); Gye and Purdy (1934); and Andrewes). Andrewes observed that pheasants, into which the chicken tar tumors could be inoculated successfully, developed antibodies which would neutralize the virus of Rous sarcoma no. 1. This investigator concluded from this evidence that tar fowl sarcoma contains a virus, though this cannot be directly demonstrated by infections with filtrates.

Andrewes, Ahlström, Foulds, and Gye; and Ahlström and Andrewes found that the intravenous injection of the rabbit fibroma virus (Shope) into rabbits, which had previously received a single intramuscular injection of tar, resulted in a generalized fibromatosis, an effect never obtained before with the virus only, and caused in one instance a polymorphous cell sarcoma. The spontaneous regression normally occurring in these virus fibromas was much delayed in rabbits which were inoculated intradermally or subcutaneously with the virus after an intramusclar injection of tar.

Very detailed and extensive experimental studies on the interrelation between the cancerigenesis by tar and the action of the Shope papilloma virus have been carried out by Rous and his coworkers, Beard and Kidd. Kidd and Rous observed, after the intravenous injection of the Shope papilloma virus into rabbits whose ears had been tarred previously for a period of 1.5 to 3 months, that there was a rapid development of numerous papillomas in the tarred areas. Some of the neoplasms were malignant, while the ears of tarred control rabbits showed only warts, which receded spontaneously later on. The investigators concluded from this evidence that the virus activates tar warts and may convert some tar papillomas into malignant ones, depending upon the localization of the virus in the skin. The virus acts in this connection, according to Rous, only in an adjuvant capacity, by exerting a driving and formative effect upon the cells rendered neoplastic by tar. Rous argued that as tar cancer cannot be produced at will, because this neoplasm affects only relatively few places in large areas subjected to the carcinogenic stimulation, as the incidence of tar cancer varies notably from individual to individual, as their origin is punctate, and as no experimental procedure thus far employed has caused them to appear as diffuse processes or in unexampled multitude, though their number may increase with continued tarring, some agent, probably a virus, must be present where tar cancers arise (indigenous virus). It was pointed out by Rous that there does not exist any serological relationship between papillomatous tumors produced by tar and those caused by virus, in spite of a close histological similarity.

This observation received support from a study of Höra, who found that the development of papilloma virus lesions was not hastened when the ears

of rabbits were tarred before the inoculation of the virus, and when an intoxication with tar was produced before a tar tumor immunity or atrepsy had a chance to develop. The papillomas caused by the virus exhibited a peculiar type of myxomatous degeneration.

A critical evaluation of the evidence presented permits the conclusion that the mere presence of a virus in tumor tissue is no proof that the virus has any direct causal relation to the neoplasm or its development, as viruses may infect cancerous tissue produced by the action of exogenous agents, such as tar and synthetic chemical carcinogens without exerting any specific effect other than that elicited in normal tissue (Pearce and Rivers; and Mellanby). Until more evidence for the existence of a virus in tar cancer is obtained, Rivers counsels us not to take the suggestion too seriously that a latent virus acts in conjunction with the tar in the production of malignancy and is responsible for the continuance of the growth even after the tarring has been stopped. Similar objections against such contentions were expressed by Murphy. Rous' claim, that the punctiform origin of tar cancer favors the presence of a virus in the affected cells, disregards the fact that an atypical transformation of the epithelium of the skin or mucous membranes under the influence of carcinogenic chemicals or physical agents, is not infrequently of a more or less diffuse character, which has an analogy in the so-called carcinomatous coating of certain mucous membranes.

It is obvious from a careful study of the precancerous and early cancerous lesions of experimental chemical cancers that local nutritive vascular conditions may greatly influence the realization of a cancerous response, without necessitating the assumptive presence of a hypothetical virus. A localization of reactive manifestations, following general exposures to a causative agent, is scarcely a proper reason for suspecting the presence of a virus, as allergic reactions do not always involve an entire organ or organ system, but sometimes remain restricted to certain parts or multiple foci of one organ (Doerr).

The evidence available at the present time suggests that certain viruses are the cause of several well-defined types of tumors, and represent biologically active agents which resemble in their chemo-immunological behaviour that exhibited by protein complexes of carcinogenic, polycyclic hydrocarbons (Schlesinger). The investigations of Stanley have shown that the virus of the Shope papilloma is a macromolecular protein, possessing antigenic properties. The antibodies formed by the organism in response to the carcinogenic viruses are capable of neutralizing the viruses contained in the tumor filtrates by becoming adsorbed to their surfaces (Burnet, Keogh, and Lush), revealing qualities identical with those possessed by the previously mentioned chemo-immune bodies, which act upon the polycyclic hydrocarbon-protein complexes. The mere fact that tumor viruses are antigenic does not mean that an extraneous agent is present in the tumor cells (McIntosh), as such a quality is possessed, for instance, by lens protein as well as other types of special tissue proteins (spermatozoa and leucocytes).

Stanley, who isolated the virus protein of the Shope rabbit papilloma virus in a crystalline form, expressed the opinion that this virus protein is a pathological protein formed autocatalytically by the cells. It corresponds in general character to the pathological proteins generated in an organism, as reaction products (antibodies) to infections (Hughes), and its production is analogous to the autocatalytic synthesis of enzymatic biocatalysts from inactive protein molecules (Von Euler). This ability of cells to synthesize clearly defined proteins in their normal or pathological metabolism, and to transmit this property through cellular inheritance cannot be explained in any other way than through the assumption that organizers are required for the synthesis of proteins (Bergmann and Niemann). It is apparently by such a chain of events that virus proteins enter into the cellular metabolism, and may even undergo in this course mutations (Stanley).

One may define carcinogenic viruses as cellular, ready-made, carcinogenic, protein complexes which have acquired, through the special circumstances surrounding and conditioning their development, tissue specific properties, such as possessed normally by protein components of many types of tissues. The isolation of macromolecular proteins from chick embryo extracts has shown that macromolecularity is not a characteristic quality of virus tumor proteins (Stern and Duran-Reynals). The differences in the chemical composition of the Shope tumor virus protein (consisting of nucleic acids and proteinic matter in a ratio similar to that prevailing in nucleo-proteins) and the virus proteins of Rous sarcomas and fowl leucoses (thymonucleic acid and proteinic matter in a ratio similar to that of the cytoplasmic proteins) suggest different sources of origin and different types of tissue affinities, resulting in different varieties of tumors.

An allergic theory of cancerigenesis possesses the advantage that it can be coordinated with a virus genesis in a much more plausible way than any of the other theories advanced. The failure to recover the papilloma virus from malignant growths resulting from its inoculation into domesticated rabbits does not militate against this conception, as similar difficulties are encountered in the isolation of allergic immune bodies, in those types of allergies characterized by cellularly fixed reaction products (Michael; and Urbach).

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XIV

MEDICOLEGAL AND PUBLIC HEALTH ASPECTS

1. MEDICOLEGAL ASPECTS

A. Occupational Tumors

AS THE government is charged with the safeguard of the health of the people, the state is properly concerned in every aspect of occupational disease: preventive, curative, forensic, sociological, and financial. Industrial accidents and diseases resulting in the development of precancerous and cancerous conditions have been made the subject of legislative action in numerous countries. These considerations resulted in the establishment of industrial accident insurance laws, workmen's occupational disease compensation laws, and industrial safety codes regulating and controlling the working conditions in industry. The first attempts made in this direction are represented by the various royal decrees issued in England during the early parts of the nineteenth century, regulating the age of the apprentices and the working conditions of the chimney sweeps' trade so as to curtail the occurrence of scrotal cancer among the sweeps.

This small and feebly enforced beginning of industrial health legislation in regard to occupational cancer was followed, in 1884, by the first comprehensive national scheme for providing compensation to injured workmen, enacted in Germany (German Industrial Insurance Act). The compensation laws covering industrial accidental injuries passed subsequently in other countries were patterned after the German laws, but were not, in many instances, as far reaching and comprehensive as the German original. These early laws afforded protection and compensation only for neoplasms arising from or related to accidental industrial injuries. They did not cover the more important and frequent cancers caused by exposure to certain occupational agents. The inclusion of the occupational tumors proper in the workmen's compensation laws is a relatively recent development, dating back no more than twenty years, when laws were passed in many countries adding occupational diseases to the list of compensable disabilities arising out of injuries sustained during work.

Following the enactment of a federal compensation law in 1908, applying only to the relatively few employees of the United States government engaged in hazardous occupations, all but two states (Mississippi and Arkansas) have passed laws providing compensation to workmen for industrial injuries (Koontz). There are at the present time only twenty-four states which possess some kind of compensation law covering occupational diseases in general or of

certain types. The remaining twenty-four states have not yet recognized in their laws that an employer is liable for the diseases workmen contract as the result of the conditions of their employment. Only nine of the states with compensation laws for occupational diseases have general or blanket coverage laws, which cover any diseases that can be shown to be of occupational origin, and therefore all types of occupational and accidental industrial neoplasia (as of January 1, 1939) [California, Connecticut, District of Columbia, Illinois, Indiana, Massachusetts, Missouri, New York, North Dakota, and Wisconsin (Sappington; Waters; Foerster; and Koontz)]. Delaware, Kentucky, Michigan, Minnesota, Nebraska, New Jersey, North Carolina, Ohio, Pennsylvania, Rhode Island, West Virginia, and Washington have so-called schedule coverage laws, which apply to a varying number of specifically named occupational diseases, and include only a restricted number of occupational tumors or none at all, depending on the type of laws enacted in the different states. Some of the states of this group have limited the applicability of the compensation laws still more by naming the type of operation or occupation from which the given industrial disease must arise to be compensable (Newquist). The substances which upon an occupational exposure may cause cancers, as well as the states in which such occupational neoplasms are included in the schedule coverage, are presented in the following list:

LIST OF CARCINOGENIC SUBSTANCES AND STATES WITH SCHEDULE COVERAGE LAWS COVERING DISEASES CAUSED BY THESE AGENTS

Substances:	
Arsenic	Delaware, Michigan, Minnesota, New Jersey, North Carolina, Ohio, Pennsylvania, Rhode Island, and Washington
Asbestos	North Carolina and Pennsylvania
Benezene, its homologues and derivatives	Delaware, Michigan, Minnesota, New Jersey, North Carolina, Ohio, Pennsylvania, Rhode Island, and Washington
Tar, pitch, bitumen, mineral oil, paraffin, and any compound, product, or residue of any of these substances	Michigan, Minnesota, North Carolina, Ohio, Pennsylvania, Rhode Island, and Washington
Nickelcarbonyl	Michigan, Minnesota, and Rhode Island
Radium-Mesothorium	Delaware, Michigan, New Jersey, North Carolina, Ohio, Minnesota, and Rhode Island
Roentgen-rays	Michigan, North Carolina, Minnesota, and Rhode Island

The compensation laws in force in other countries mention the following substances, which may be the cause of neoplastic diseases (International Labour Conference, 18th Session, Rep. V):

Australia: arsenic; and benzol and its homologues, or their nitro- and amino-derivatives. Similar laws, including tar and pitch are enacted in the various states of the Dominion of Australia.

Belgium: arsenic; benzol, its homologues and nitro- and amino-derivatives; radioactive substances; roentgen-rays; and tar, pitch, bitumen, mineral oil, paraffin, or all compounds, products, or residues of these substances.

Bolivia: hydrocarbons.

Brazil: arsenic; and hydrocarbons.

Bulgaria: arsenic; and hydrocarbons.

Canada: arsenic; lubricating oils; and benzol and its nitro- and amino-derivatives.

Chile: arsenic; hydrocarbons; and tar and derivatives.

France: roentgen-rays; radioactive substances; aniline and derivatives; arsenic; pitch; tar; mineral oil; and bitumen (Duvoir; and Florentin).

Germany: arsenic; aromatic amines; soot; paraffin; tar; pitch; anthracene; chromate; roentgen-rays; and radioactive substances (Martineck).

Great Britain: arsenic; nitro- and amido-derivatives of benzol and its homologues; tar; pitch; bitumen; mineral oil; paraffin; or any compound, product, or residue of any of these substances; soot; roentgen-rays; and radioactive substances. Especially mentioned: chimney sweeps' and mule-spinners' cancer.

Italy: aromatic amines.

Japan: arsenic; and tar.

Mexico: thermic heat; solar rays; roentgen-rays; radium; arsenic; paraffin; and tar.

Russia: amino derivatives of benzol, tar, and naphtha.

Sweden: arsenic; roentgen-rays; and radium.

Switzerland: aniline and homologues; arsenic and compounds; benzidine; benzol; dianisidine; tar, its gases and oils; pitch; and radium and its compounds (poison list) (Barkmeyer).

Porto Rico: arsenic; benzol and derivatives; and tar.

Carozzi compiled the following list of the various carcinogenic agents and cancerous manifestations included in the different countries in their compensation laws:

Epithelioma of the Skin:

Anthracene: Germany.

Asphalt: Rumania and Venezuela.

Bitumen: Argentina, Belgium, Cuba, Britain, Ireland, and several states in the United States (states with blanket laws; Minnesota and North Carolina).

Tar: Germany, Argentina, Australia (West Australia and Queensland), Belgium, Canada (Ontario), Cuba, Great Britain, Ireland, Russia, Venezuela, and several states in the United States (states with blanket laws; Ohio, Minnesota, and North Carolina).

Pitch: Germany, Argentina, Australia (West Australia and Queensland), Canada (Ontario), Cuba, Finland, Great Britain, Ireland, Rumania, Russia, Venezuela, and several states in the United States (states with blanket laws; North Carolina and Minnesota).

Mineral oils: Argentina, Australia (West Australia and Queensland), Belgium, Cuba, Great Britain, Ireland, Rumania, Venezuela, and several states in the United States (states with blanket laws; North Carolina and Minnesota).

Paraffin: Germany, Argentina, Belgium, Great Britain, Ireland, Rumania, Russia, and several states in the United States (states with blanket laws; North Carolina and Minnesota).

Petroleum: Rumania and Venezuela.

Soot: Germany, Russia, and several states in the United States (states with blanket laws; Ohio).

Resins: Rumania

Anthracite: Russia

Epitheliomatous cancer without reference to site, due to contact with tar, paraffin, and related substances: Mexico.

Papillomatous or keratotic neoplasms of the skin, caused by contact with mineral oil in cotton spinning plants: Great Britain.

Epithelioma of scrotum of chimney sweeps: West Australia, Great Britain, and Ireland.

Epitheliomatous ulceration of cornea of eye due to contact with: 1. tar, pitch, mineral oil, or products containing one of these substances: West Australia and Queensland.

2. Bitumen: Ireland.

3. Bitumen and Paraffin: North Carolina and Minnesota.

4. Soot, tar, and pitch: Ohio.

Cancer of the Lung: Schneeberg and Joachimsthal, Germany; Chromate: Germany.

Cancers of the urinary bladder caused by aniline and aromatic amines: Germany, Italy, Australia, Belgium, Canada, Cuba, Great Britain, India, Ireland, Norway, Venezuela, Switzerland, Russia, North Carolina, Minnesota, New Jersey, Ohio, Porto-Rico, and those states in the United States having blanket coverage laws.

Cancerous lesions produced by roentgen-rays: Germany, Argentina, Australia (Queensland), Belgium, Bulgaria, Cuba, Finland, Great Britain, Ireland, Mexico, Norway, Peru, Portugal, Rumania, Sweden, Russia, Switzerland, North Carolina, and those states of the United States which have blanket coverage laws.

Cancerous lesions resulting from occupational contact with radioactive substances: Argentina, Belgium, Cuba, France, Germany, Great Britain, Ireland, Mexico, Norway, Portugal, Rumania, Sweden, Russia, North Carolina, New Jersey, and those states of the United States possessing blanket coverage laws.

The above list of compensation laws enacted in the various countries and states reveals a remarkable lack of uniformity as to the number of occupational neoplasms and carcinogenic agents covered. While local differences in the types of industries present in the various countries account for some of these discrepancies, others represent serious inadequacies in the compensation laws of a given country.

The divergence observed between the scope and character of these laws in force in different countries becomes still more marked, if an analysis is made

of the detailed wording, limitations, interpretations, and administration of these legislative measures. Inadequate, inequitable, and ambiguous compensation laws, permitting varying constructions and interpretations to be placed upon them by different courts, have resulted, in an appreciable number of instances, in a condition interfering with their efficient and speedy enforcement. They have proved expensive for the employee who has contracted a neoplastic growth of occupational genesis and is trying to collect compensation and for some industries and their insurance carriers, as the uncertainties of legal interpretations of such laws, which carry a high financial liability with them in view of the serious and prolonged character of neoplastic diseases, constitute a constant hazard to the financial security of the employers (Foerster). The lack of uniformity of compensation laws in the various states of the United States interferes seriously with the fixing of responsibility for such cases, in which the occupational neoplasia is caused by an industrial exposure sustained in several positions occupied in different states.

The inclusion of clauses limiting the time of liability by the employer for occupational diseases and disabilities appearing after the cessation of employment is particularly inequitable in connection with industrial neoplasms. While the time clauses inserted in many compensation laws specify periods ranging from 6 months to 6 years (for the majority of industrial diseases from one to two years in most countries), these time limits are obviously entirely insufficient in regard to occupational cancers, which may develop twenty years and more after the carcinogenic industrial exposure has ended. This consideration appears to be especially important, as it is an obvious fact that the time interval between cause and effect in occupational cancerigenesis is frequently so long that the etiological interrelation is easily obscured and not recognized, to the disadvantage of the afflicted individuals (Burrows, Mayneord, and Roberts).

An additional defect present in many laws is represented by an inadequate definition of the particular carcinogenic agent or agents responsible for certain malignant manifestations. The compensation laws enacted in Switzerland and New Jersey, for instance, name only benzol, benzol derivatives, and homologues as agents which may cause compensable cancerous lesions in the urinary bladder, omitting naphthalene derivatives which exert the same effect. In Switzerland this apparent injustice is neutralized by the fact, that the industrial commission adjudging cases of industrial diseases is vested with the authority to extend the benefits of the laws to cases which are obviously of industrial origin. Consequently, it is customary in Switzerland to include as a matter of course bladder cancers produced by an exposure to naphthylamines under the compensation laws. Similar conditions exist in many countries in regard to the various radioactive substances and the coverage of the malignant lesions caused by them.

The schedule coverage laws, through which the compensability of occupational cancers is limited by restrictions placed upon the type of causative agents,

the character of industrial operations in which the neoplastic diseases can be contracted, and the nature of the occupational disease to which the law is applicable, are becoming more and more objectionable, obsolete, and inadequate, especially in view of the rapidly expanding chemical industry. This industry furnishes the great majority of occupational cancers, and extends the use of the number of known industrial carcinogenic agents to more and more operations and purposes, adding continuously, at the same time, new substances of unknown and unpredictable biological qualities to those substances already industrially produced and employed. The deficiencies and inequities of compensation laws adopted in certain states, together with a change in our concepts of social justice, have led sometimes to judicial constructions in the interpretation of these laws, in order to determine the liability of employers and to grant financial benefits to the claimants, which go beyond or deviate distinctly from the original intent of the laws. Compensation laws applying to industrial accidents only have thus been used to cover occupational diseases including cancers, by considering them as the result of a series of industrial accidents.

The evidence presented and the information available concerning occupational neoplasms indicate clearly that blanket compensation laws, properly administered, provide the most efficient, adequate, and fair coverage of these important and serious industrial diseases. Wherever such laws have failed to accomplish this end, it has not been the fault of the law, but of its practical application by unsuitable or inexpert individuals. The administration of these laws is often left, at the present time, in the hands of persons unfamiliar and inexperienced with the highly complex and specialized character of etiological agents, causative mechanisms, and exposures leading to the production of industrial cancers.

The circumstances surrounding the development of occupational tumors make it advisable to turn over the administration of compensation laws dealing with these diseases and their precursor conditions to a group of experts in medicine, industrial hygiene, and engineering (physicians, pathologists, toxicologists, chemists, physicists, and industrial engineers), which should be made an integral part of the compensation court, working with and not under the representatives of the legal profession (Martland). Such a body of competent men can be relied upon to render unbiased judgments as to the occupational nature of a given tumor on the basis of existing knowledge, and to prevent any abuses which may otherwise arise from the administration of a law which is as flexible and adaptable as the blanket coverage law. These experts may act with advantage as consultants to the department of labor, and they can also give competent advice concerning the intelligent administration and modification of the existing labor laws covering the working conditions in the various industries which cause industrial neoplasms. Such a body may be of invaluable service in the eradication of these preventable occupational diseases.

B. Accidental Traumatic Tumors

While the medicolegal aspects of occupational neoplasms proper are relatively simple considering the well-defined and clearly established etiology for most of these diseases, a great deal of confusion and controversy exists in regard to the causation and, therefore, the compensability of accidental, traumatic, industrial tumors. The relation of an occupational trauma to a cancerous condition may assume one of the following five forms:

1. An accidental injury may be incriminated as the direct or indirect cause of a malignant growth arising in a tissue, which was apparently normal prior to the accident.

2. An accidental injury may be superimposed upon a pathologically altered tissue, affected by some kind of noncancerous condition of occupational or nonoccupational origin, and may bring about a malignant transformation of the cells in the traumatized area.

3. An accidental trauma may involve a preexisting cancer, either present as a dormant growth which responds with an activation of its proliferative potentialities, or existing as a manifest malignant growth which reacts with an acceleration of its local and metastatic growth activities, thereby hastening its course and aggravating its prognosis.

4. An accidental trauma, while not involving a preexisting cancer directly, may lower the general vitality and resistance of the affected individual to such an extent, that the impairment of the general health interferes with the timely application of therapeutic procedures indicated and necessitated by the cancerous disease, or aggravates appreciably the dangers connected with such procedures, reducing the normal prospects of cure or life expectancy.

5. The pathological conditions created at the site of an accidental injury may favor the colonization of tumor cells, originating from a cancer remotely located from the traumatized area.

Exceptionally, a therapeutic trauma, sustained during the treatment of a non-neoplastic, industrial disease, may give rise to the formation of a cancer, which becomes a malignant tumor of accidental industrial genesis. Such an instance was reported by Saunders and Montgomery, who observed two roentgen-carcinomas of the skin in workers exposed to roentgen-rays administered in the treatment of an industrial dermatosis.

The above list shows that an accidental injury may play a primary direct or indirect causal role in the production of a cancer, or it may exert a secondary, contributory influence upon the development or course of a cancer, when being superimposed upon some kind of primary preexisting, non-neoplastic, preneoplastic or neoplastic disease condition. Medical expert witnesses frequently disagree with each other, the courts, and compensation boards concerning the probable connection between an accidental injury and the causation of a given cancer or its influence upon the course of a preexisting malignancy.

The chief medical controversy, which centers around the question whether

or not a single trauma may elicit in a previously normal tissue, within a relatively short period (a few weeks), a malignant neoplastic reaction (immediate carcinogenic effect), is of great medicolegal importance, as the courts and industrial commissions of American and European states have recognized single trauma as a competent producing cause of all types of malignant tumors. Von Hansemann; Orth; Teutschlaender; Knox; Brosch; Davis; Fowler; Sauerbruch; Segond; Roussy; Barkmeyer; and Ewing have seriously doubted or entirely denied the possibility, that a single trauma affecting a normal tissue ever gives rise to an acute cancer. It is through their influence that the recognition of such a relationship by compensation boards has become increasingly rare during recent years. The increasing knowledge concerning the etiological factors controlling or influencing carcinogenesis makes it more and more difficult to conceive on scientific grounds that a nonspecific tissue injury may produce within a short time a malignant growth in a previously normal tissue. Wainwright pointed out that admitting the existence of such a relationship even in one case necessitates its being considered in any other case in which a traumatic etiology of a cancer appears to be present from the evidence available.

The following objections are raised against such a relationship (Barkmeyer): 1. All attempts directed toward an experimental production of traumatic cancers have failed. 2. Trauma plays no appreciable etiological role in the development of spontaneous tumors in animals. 3. Malignant neoplastic sequelae have never followed a surgical trauma. 4. The contrast between the incidence of traumas and that of allegedly traumatic cancers is too great for assigning to the accidental injuries any significant part in the production of malignant tumors. 5. The experiences gained in this respect from the numerous accidental injuries sustained during the World War contradict the contention of an acute traumatic effect of neoplastic nature. 6. Cancers are relatively rare at sites frequently traumatized (palms of fingers and hands, soles of feet, buttocks, knees, and elbows).

It must be conceded that the first of the several objections listed is essentially correct. Lewin tried, in vain, to cause tumor formations in the ears of rabbits, by combining injections of scarlet red with hammer blows to the treated area. Boyland and Burrows produced an inflammatory focus in rats by the injection of silica into the nape, and then introduced subcutaneously or intraperitoneally an aqueous colloidal solution of 1.2.5.6-dibenzanthracene. They could not obtain tumors in the traumatized tissue. Similar experiments with rabbits were equally negative. Ribbert caused in rabbits, by a stab into the intervertebral discs, a proliferation of the chordal tissue, which regressed spontaneously after some time. Shear found that the application of mechanical trauma to the site where methylcholanthrene had been injected exerted no favoring effect upon the tumor formation, and there was even some evidence that this procedure interfered somewhat with the genesis of the neoplasm elicited by a synthetic carcinogen.

Fischer, on the other hand, reported that a traumatic disturbance of a normal healing process, obtained by a frequent auto-transplantation of mammary tissue in pregnant mice, resulted in the production of mammary cancers. Malignant tumors appeared sometimes after the first transplantation. The genetic properties of the mice used, the reactive vascularizations of the transplanted tissue, and the physiological congestion of the mammary tissue present during pregnancy may have played an important causal role in bringing about these extraordinary results. The existence and possible importance of a genetic neoplastic predisposition in the development of traumatic tumors is suggested, though by no means proven, by an observation of Slye, who described 87 sarcomas, developing presumably at sites of former injuries, in genetically predisposed mice.

The second objection listed is open to question, as no reliable and extensive data exist on which such a claim could be reasonably based, with the exception of the rather doubtful data furnished by Slye.

The third objection can be regarded as essentially correct, as there is indeed no record of a cancer formation occurring at the site of a surgical trauma. The fourth objection represents mainly an argument based upon a statistical reasoning of obvious facts. Metz, for instance, recorded that during 20 years with 150,000 injury cases reported to the claim department of the Milwaukee Railroad, there was never a lawsuit in which a claim of a traumatic malignancy was made. In the study of a series of over 50,000 fractures and lacerations made by this investigator, there was not a single case of traumatic malignancy noted. Lewy, from records of the New York State Industrial Compensation Board, found only 37 cases of malignant tumors among 26,389 injured persons. In only a few of these neoplastic cases could a posttraumatic origin be established. The observed ratio was 1 to 700 or approximately that of the general population at the age of 50 (Davis). Ewing stated that French medicolegal experts noted the occurrence of as low as 5 to 6 traumatic tumors among 100,000 injuries. Martland cited Kessler to the effect that only 19 of the 56,000 cases with industrial injuries handled by the New Jersey Workmen's Compensation Bureau made claims that a malignancy was a sequela of a trauma sustained. Of these 19 cases only 6 cases were fairly well proven. Ackermann noted that among the 30,000 cases handled by the Swedish accident agency, only 4 recognized traumatic tumors were listed.

Similar evidence supports the fifth objection recorded. Von Hansemann stated that from the experiences of the World War, there occurred neither an increase of tumors nor an appearance of new types of cancers. A similar opinion was expressed by Hauser as well as by Schad, who emphasized that these experiences necessitated a more critical attitude toward a traumatic causation of tumors. Fischer-Wasels pointed out that the experiences of the World War represented an unsuitable object, and therefore did not decide the question concerning the etiological significance of trauma in carcinogenesis. Fischer-

Wasels argued that if in the war only individuals of 60 years or more had participated, there would have been most probably a different outcome of this experiment, that is, an increase of tumor formation, while only of a minor degree, would have occurred. There is indeed some evidence supporting such a conclusion, while other data contradict it.

Hauser mentioned 8 cases of malignancy following war injuries (Werner; Schad; Blumenthal; Just; Albu; Iselin and Maier), which seemed to be acceptable. Luckow added two more cases of this type, both occurring after a prolonged latency period. More recently, Scheid collected all cases published in the German literature concerning the development of malignant tumors in gunshot wounds. There were 33 such cases (11 sarcomas, 13 carcinomas, and 7 brain tumors), of which 22 had occurred in connection with injuries sustained during the World War. Scheid supplied the information that with 3,710,371 gunshot wounds treated in German hospitals, 5.3 malignant tumors were observed per 1 million cases. This ratio was very much less favorable in connection with brain lesions, as there were 4 tumors per 10,000 brain injuries. Körbler as well as Pohl recently recorded additional cases of malignancy after gun shot wounds, while Reymann pointed out that an increase of cancer on the basis of old war wounds, especially in the form of fistula cancers and scar carcinomas, has been noted during recent years, i.e., approximately 25 years after the end of the conflict. Nevertheless, the relative rarity of cancerigenesis on the basis of gunshot wounds is strikingly demonstrated by these figures.

In contrast to the contention of Fischer-Wasels, that old individuals have a higher liability to develop traumatic cancers than young ones, Werner; Ophüls; and Schad asserted that traumatic neoplasms were found mainly in individuals belonging to the younger age groups, while Hauser noted their occurrence most often in persons of middle age. It may be doubted, whether the age factor possesses in this respect any actual significance, as a traumatic etiology is alleged unusually often for neoplasms occurring normally during the earlier periods of life (bone sarcomas, testicular carcinomas, and cerebral gliomas).

The sixth objection mentioned is correct when judged from a general statistical basis, but its intrinsic value becomes doubtful, if it is remembered that there exists a certain amount of evidence, indicating that individuals subjected to frequent occupational traumatization of the hands, fingers, and soles show an excessive incidence of cancers at these sites. It is naturally impossible to determine from such data the possible role which a single trauma, perhaps in connection with specific factors, may have played in such cases in bringing about a malignant tissue response.

In view of the uncertainties connected with the scientific and medicolegal appraisal of the causal role, which a trauma might play in the development of a cancer, several investigators (Segond (1907); Thiem (1909); Blumenthal

(1930); Ewing (1935); Brocx (1931); Koelsch; and Knox) laid down a series of postulates, the fulfillment of which was considered essential for the recognition of a primary traumatic genesis of a cancer. The following theses were advanced for this purpose:

1. The workman's accident and injury must be established with moral certainty, and the injury must be due to force and not shock or fatigue (authenticity of the trauma). The information concerning the type of the accident and in regard to the site and character of the injury sustained must be obtained from the claimant as soon as possible after the accident, and must be confirmed, if possible, by reliable witnesses. The immediate effect of the injury should be ascertained and recorded as early as possible by a physician, in order to avoid the possibility that a much delayed notification opens the way to biased and uncontrollable statements from the interested party.

2. The absolute intensity of the trauma is less important than the tissue effect produced by it, which must be sufficiently appreciable to cause demonstrable tissue changes, which do not necessarily need to become manifest immediately after the trauma, but may develop possibly to their full extent some time later (adequacy of the trauma). The tissue changes may be a superficial and open wound (laceration), or a more deep-seated contusion. In the latter case, there should always be evidence of at least some kind of injury to the overlying superficial parts, especially in parts where the skin is close to the bone or fixed to the deeper parts.

3. The tumor must be present either at the site of the trauma or at a place where an indirect, associated, traumatic effect appears to be possible under the particular anatomical conditions existing (counter coup in the brain and eye) (topographical relation of trauma).

4. The preexistence of a tumor at the site of the trauma must be excluded, and the previous integrity of the wounded part must be established with reasonable certainty. Physical and, where feasible, roentgen-examinations of the injured area should be made for this reason as soon as possible after the accident, so as to eliminate the presence of a small and slowly growing, preexisting neoplasm, producing no subjective symptoms at the time of the trauma. Absolute proof concerning the absence of a preexisting tumor is difficult to bring about even with such measures, as an incipient neoplasm present at the time of the accident may not cause any objective symptoms demonstrable with the applicable diagnostic methods.

5. An interval of reasonable length must elapse between the trauma and the first signs of a neoplastic growth. While it does not seem advisable to set an upper limit in this respect, as it is well known that cancers may develop in burn scars and similar lesions showing a prolonged inflammatory and regenerative activity several decades after the original accident (similar to the long latency periods observed with many occupational cancers), there must be serious doubts as to the primary etiological relation of a trauma to a

subsequent cancer, if the neoplastic development becomes manifest within a few days or weeks after the injury. The existence of a not recognized precancerous or cancerous condition at the site of the injury at the time of the accident becomes under such circumstances a matter of strong suspicion and probability. The proper consideration of the size of the tumor at the time of its discovery, its histological type, permitting an estimate of its approximate normal growth rate, and the presence or absence of metastases may be of distinct help and value in the analysis of such cases.

6. The symptoms characterizing the primary traumatic period may be connected by the so-called bridging symptoms (continuity of pain, swelling, functional disablement, suppuration, and ulceration), observed during the preparatory period, with the symptoms of neoplastic origin, found during the manifestation period of the neoplasm. The presence of bridging symptoms is not an essential feature for the establishment of a causal relationship between trauma and cancer. There may even occur pseudo-bridging-symptoms, which actually represent an indication that the trauma affected a site containing a preexisting, unsuspected cancer. This conclusion is suggested, if the symptoms elicited by the trauma appear to be out of proportion to its intensity, and lead over without any appreciable reduction into those manifestly produced by the neoplasm.

The claim, frequently made, that traumatic sarcomas require a shorter latency period than carcinomas, is scarcely tenable considering that the distinction between these two types of malignant tumors is to a large extent an artificial one, based upon morphological criteria and not upon biological or embryological-histiogenetic ones (Hueper). The data given, concerning this matter by various investigators, are, therefore, without significance from a medicolegal viewpoint (Thiem: sarcomas: 8 days to 1 year; carcinomas: 3 weeks to 3 years; and gliomas: 1 month to 10 years or more). The latency periods vary obviously in part with the average growth rate of a particular type of neoplasm (Fraenkel; Pick; and Ewing).

7. The diagnosis of a neoplasm and its type must be established definitely by proper and adequate means and by competent physicians. It must be based on clinical and roentgenological evidence, confirmed and supplemented, wherever possible, by histological evidence. The histological examination of tissue removed from the suspected lesion can provide, although not always, important information as to the histogenesis of a given neoplasm and particularly its primary or secondary (metastatic) character, aspects of considerable medicolegal significance. Whereas the histological evidence, when furnished by an experienced pathologist, must be considered as the most reliable one, there exist here sources of error or opportunities for differences in interpretation and opinion, which should be taken into account and carefully weighed in each case. Whenever such difficulties or uncertainties arise, it should be insisted upon and made obligatory that in the case of subsequent death, a

post-mortem examination is performed through which the disputed neoplastic character, its source and type, can be established in the overwhelming majority of cases beyond any doubts, providing thereby a sound basis for fixing the liability, reliably and definitely.

The medical expert, thus, depends in his evaluation of a case upon the availability of a certain amount and type of information, without which he cannot be expected to render an intelligent opinion and judgment. The medical adjudication of traumatic cancers relies upon the observation of certain general principles, which should not be followed dogmatically, as our present knowledge of the causation of malignant growths is still greatly defective. In the practical medicolegal application of the existing information in this matter, due consideration should be given to the concept of general common sense concerning the interrelation of cause and effect recognized and applied by courts and compensation boards. The decisions rendered by these agencies cannot be based purely on scientific deliberations, but must rely in part upon reasonable, circumstantial evidence, to prevent undue hardship to the afflicted individual (Woodward; Dandy; Behan; Sappington; Fenster; Fischer-Wasels; and Roussy).

If the criteria and requirements essential for a fair and just recognition of the allegedly traumatic cancers, dealt with in courts and industrial commissions for adjustment, arbitration, or litigation, are followed, there will remain only a rare case which is acceptable medicolegally, mainly because of lack of evidence to the contrary. The relatively small practical importance of acute traumatic carcinogenesis is illustrated by the fact that Büngeler was able to collect not more than 100 recognized cases of this type from all German university clinics.

Hauser, who analyzed 262 cases reported in the literature as traumatic cancers of various organs, concluded that in only 13 of them a traumatic factor entered into their etiology beyond any doubt; in 48 cases this appeared to be probable, in 94 cases such an influence was considered possible, but not probable, while in 107 cases there was definitely no causative accidental relation present. Single trauma as the primary factor in cancerigenesis is, therefore, no longer a matter of genuine interest among medical men (Knox). The medicolegal attention, which is extended to this subject to an increasing degree in recent years, is attributable, according to this investigator, to the efforts of commercial agencies, because of the increasing accessibility of compensation for any injuries sustained while in discharge of any kind of employment. In view of the higher legal responsibility of employers to employees, these are encouraged by such parties to give countenance to the idea that a tumor may have had a traumatic origin, in order to collect compensation grants.

With the scientific, while not entirely medicolegal exclusion of a single trauma as a cause of cancer in normal tissue, this principle does not greatly

reduce, in the opinion of Ewing, the medicolegal importance of an injury as an indirect cause of cancerigenesis, because the clinical evidence favoring such a connection is too substantial in many cases to be dismissed on theoretical grounds. Trauma as an indirect, contributory, or aggravating cause of cancerous disease has received increased attention during recent times for scientific and medicolegal reasons. In an attempt to offer some plausible explanation on this basis for the occurrence of those acute traumatic cancers, which are supported by reliable and adequate circumstantial evidence, the postulate was advanced that a single trauma may elicit, as a precipitating factor, a neoplastic development from a prepared soil (Barkmeyer; Ewing; Teutschlaender; Brosch; Moran; Leclerq; Dietrich; and Pentimalli). The presence of a general or local neoplastic predisposition, such as a congenital or acquired precancerosis, a tissue malformation or misplacement, dysontogenetic foci, or chronic inflammatory, metaplastic processes at the site of the injury were considered as sufficiently important to serve as a basis in which a trauma may be capable of initiating tumor formation. Teutschlaender noted that the existence of such a latent disposition may not always be associated with a grossly visible lesion, but may be of purely microscopically demonstrable nature.

Barkmeyer; and Teutschlaender argued that, according to this conception, a single trauma followed by an acute cancerous neoplasia should not be considered medicolegally as more than an accelerating factor acting upon a preexisting tumor anlage, which sooner or later would have been activated and acted upon anyway by some exogenous agent of some kind.

A critical evaluation of these premises and their medicolegal implications shows that they can be accepted only with marked reservations. It is entirely unproven that individuals possessing an alleged general neoplastic diathesis (which is a hypothetical conception) would react to the tissue injury caused by a single trauma with the development of a cancer. There is no evidence indicating that an excessive incidence of cancerous manifestations is present in the families of persons suffering from a malignant tumor of an alleged traumatic genesis. Apart from the fact that it will be near to impossible to demonstrate macroscopically or microscopically, in most cases of traumatic malignancy, the presence of a local predisposing lesion of congenital origin, such as a tissue malformation, misplacement, or rest, there exists no reliable evidence supporting the conception of a possible malignant transformation by the action of a single, nonspecific trauma (Ewing; and Simon), unless the tumors are of a type attesting through their structure such a dysontogenetic origin.

It is well-known that postfetal tissue misplacements, such as traumatic epithelial cysts, scarcely ever form the basis of a cancerous development. The same applies to experimental tissue misplacements resulting from implantations (Ribbert; Zahn; Birch-Hirschfeld and Garten; Ewing; Kaufmann; and

Schweniger) or from transplantations (Cohnheim and Maas; Fischer; Leopold; and DeJong and van der Kemp). There exists a certain amount of clinical and experimental evidence indicating that occupational and experimental precanceroses caused by tar, mineral oil, paraffin, roentgen-rays, and thermic burns may be stimulated into a precocious malignant transformation by the action of a single trauma (Deelman; Cramer; and Moran). In spite of the meager data supporting a predisposing role of most of the factors incriminated as forming the basis of acute traumatic cancers, it appears reasonable to assume that some such mechanism must be present in those cases in which a single trauma to an apparently normal tissue is followed almost immediately by a bona fide cancer.

Serious doubts must be expressed concerning the justification of the medicolegal conclusions based upon such a supposition. Conceding the claim that under the circumstances the trauma accelerated a cancerous development, which was potentially preformed, there remains the question, whether or not such a course was an inevitable one without the intervention of a trauma. Sauerbruch, commenting on this subject, stated that individuals with a cancerous predisposition may remain free from neoplastic manifestations, if no external influences, such as represented by a trauma, interfere with the normal course. It is, moreover, well-established that only a relatively small number of the numerous precancerous lesions found in various occupational canceroses actually become malignant, indicating that, without an additional realization factor, their malignant potentialities may remain dormant.

If Ewing; Teutschlaender; and Barkmeyer contend that a trauma merely precipitates the development of tumors in tissues which are on the point of yielding them spontaneously due to the presence of a precancerous condition of long standing, and that the recognition of such conditions by the courts calls for granting only a partial compensation, these investigators may underestimate fundamentally the essential direct role which a trauma may possibly play in bringing about neoplastic manifestations in the presence of precancerous changes at the site of the injury.

Claims concerning a causal relationship between trauma and cancer are on considerably firmer grounds from a scientific as well as medicolegal viewpoint, if a traumatic injury is followed by the development of a chronic inflammatory, or suppurative condition, on the basis of which the malignant growth ensues. While the exact mechanism of such a neoplastic development is still unknown, there can be no doubt that such a course of events may occur, as such a sequela is a fact attested by numerous, well-established clinical observations. It is immaterial from a medicolegal standpoint that a malignant sequela results in only a small fraction of chronic inflammatory traumatic lesions and that a neoplastic outcome cannot be foretold. It appears even likely that the malignant transformation in a hyperplastic or metaplastic inflammatory tissue may be brought about by the action of a secondary, exogenous or endogenous,

carcino-specific factor. Nevertheless, the fundamental fact remains that the lesion caused directly by the trauma provides, in such cases, the initial change, and thus furnishes the basis which makes possible the neoplastic formation.

There does not exist any unanimity among medical experts regarding the question, whether or not a trauma may cause an aggravation of a preexisting cancer, which can be regarded as of medicolegal significance and thus of compensable nature. Fowler, for instance, contended that an injury to a preexisting malignant neoplasm may stimulate the production of metastases only at such an advanced stage of the neoplasia that no alteration in its course results, and that neither clinical nor experimental evidence supports the claim that the growth rate of a cancer can be accelerated by a trauma.

The majority of investigators concedes that a medicolegally important aggravation of a preexisting tumor may be effected by a trauma in various ways (Ewing; Knox; Dietrich; Werner; Mock and Ellis; and Barkmeyer). A traumatic rupture of the capsule of a tumor may facilitate its local and possibly its metastatic spread, making therapeutic measures more difficult to perform and less effective in their curative results. Such untoward effects, caused by a traumatic break of the capsular continuity, are known to occur in connection with salivary gland tumors, ovarian cystadenomas, and medullary osteogenic sarcomas. A trauma to a preexisting tumor, such as especially angiomas, and other highly vascular neoplasms, may produce a severe hemorrhage followed by anemia and possibly death.

The impact of an external force upon a neoplasm of benign or malignant nature may result in intratumoral necroses and hemorrhages, which, in turn, may give rise to systemic toxic reactions, caused by the resorption of poisonous protein degradation products as well as to an acceleration of the growth rate of a cancer, evidenced by a crowding of mitotic figures in the neighborhood of the hemorrhagic and necrotic foci. The reactive hyperemia and edema following a traumatic insult, and the traumatic production of an infection of the tumor tissue facilitate the infiltrative and metastatic spread of the neoplastic cells, so that a direct traumatic action exerted upon a malignant tumor may be followed by an explosion-like appearance of metastases and a wild-fire-like growth of the primary neoplasm (Tyzzer).

The existence of a traumatic aggravation of malignant tumors is confirmed by a number of experimental observations. Knox, for instance, noted that a forceful massage of a mammary cancer stimulates metastatization. An increase in the growth rate of tumors in mice was observed by Marsh, after a mechanical crushing of larger neoplasms, while smaller tumors revealed only insignificant effects. Lubarsch, on the other hand, did not notice any changes in the normal or average growth rate or in the structural characteristics of neoplastic tissue (sarcomas of mice and rats and epithelioma of dogs) traumatized by hammer blows, crushed with a forceps, or injected repeatedly with homologous or heterologous blood.

The medicolegal evaluation of an allegedly aggravating effect exerted by a trauma upon the course of a cancer must give proper consideration to the fact, that there occur normally variations in the growth rate of malignant tumors, and that a shower-like appearance of metastases is observed occasionally without the stimulus of an external force, especially, for instance, in connection with malignant melanomas. A traumatic aggravation of a given tumor should be recognized only, if there occur harmful effects which are not observed normally. It seems safe to state that a trauma which may aggravate the course of a tumor is in general severe. This conception finds ample support in the fact that biopsies performed on malignant tumors as an accepted diagnostic procedure cause only exceptionally an acceleration of the local or metastatic growth of neoplasms (Ewing; Hellwig; and Epstein and Fedorejeff).

If the testimony of medical experts indicates that the evidence available, in a given case of traumatic aggravation of a preexisting tumor, shows, with due consideration of the normal variability in the course of neoplasms of the same type, that an incipient or well developed blastomatous condition was hastened in its course by the trauma, that no other intervening cause for the breakdown of the tumor was apparent, and that death did not result from the effects of the injury but was actually caused by it, compensation should be granted. When Mock and Ellis asserted that an employer or insurance carrier should not be held responsible for the subsequent death caused by a traumatic aggravation of a tumor as provided in the existing laws, because in the majority of cases the trauma could not aggravate the point of fatality of a preexisting condition which already positively doomed the injured patient, nor should these parties be held responsible for the hastening of such an event, for this point could only be one of speculation on the part of the medical profession, these investigators disregarded the existing knowledge concerning the natural course of the various malignant tumors.

The claim, repeatedly made, that a trauma, remote from the location of a preexisting tumor, may furnish in the injured tissue a favorable soil for the colonization of vagrant tumor cells, is based on contradictory clinical and experimental evidence. Hellner proposed the following four possibilities which may produce or simulate the existence of such a relationship: 1. the tumor cells existed by a coincidence in the tissue before the injury, and thus followed a normal developmental course; 2. the trauma caused vascular disturbances which effected an arrest of tumor cells circulating in the blood; 3. the trauma produced in the tissue metabolic changes favoring the colonization of vagrant tumor cells; and, 4. the marked regenerative processes appearing in the injured tissue favored the growth of tumor cells. Ewing considered favorably the possibility of a causal interrelation by pointing out that the traumatized capillaries might conceivably sift out vagrant tumor cells, which may find a favorable medium for growth in a hemorrhagic and devitalized

tissue, and, thus, injured tissue might facilitate the localization of a metastasis. In support of such a conception, Ewing mentioned that the occurrence of tumor emboli in the capillary lumina of the lungs and other organs, demonstrated by M. B. Schmidt, was evidence of the presence of tumor cells in the circulating blood which became lodged in the narrow vascular passages without giving rise in many instances, to metastatic growth. It appears reasonable to assume that an injured tissue provides a more favorable medium for cellular proliferation than is present in the pulmonary capillaries or splenic sinuses.

Ewing argued that since the formation of metastases occurs usually during the later stages of the neoplastic disease, a traumatic localization of a metastasis cannot have any influence on the course of the disease. Barkmeyer; and Coley and Higinbotham believed that a trauma to normal tissue may aid in a cancer carrier in the localization of a metastasis, and thus cause an aggravation. A case, reported by Firket, seems to illustrate such a connection. There developed in a woman, four years after the extirpation of a rectal carcinoma, a metastasis on the dorsum of a foot following a traumatization of this area. Similar observations were recorded by Barret as well as Siebner. Fischer-Wasels expressed his doubts concerning the existence of such relations. Hellner noted that no satisfactory evidence had been advanced in support of the stated contention, as he found, in an analysis of a large series of cancer cases, only one single case in which a metastasis developed at the site of a previous trauma, and similar observations were rarely recorded by others. A similar conclusion was reached by Burrows, who studied the localizing effects of injury upon various disease manifestations, including cancerous metastases.

Equally negative experimental results were reported by Lubarsch, who failed to demonstrate any localizing effect of a trauma upon the formation of metastases in cancer bearing mice in which fractures of bones were produced. Jones and Rous attempted to prove such interrelations by introducing into the peritoneal cavity of mice kieselguhr, dead tumor cells, and glass rods followed by the injection of tumor cells. While the injected tumor cells became implanted often in the fibroblastic tissue surrounding the foreign bodies, control animals, injected with tumor cells only, revealed frequently peritoneal implantations. The experimental conditions used in this study are very dissimilar from those existing in man under accidental circumstances. The successful production of metastases by the traumatization of any part of the body of fowls inoculated with a filtrable sarcoma (Pentimalli; and Foulds) appears to be an evidence of even more objectionable value from a comparative viewpoint, as the causative virus acts upon fibroblasts.

In evaluating the possibility of a traumatic localization of metastases, consideration must be given to the fact that we are ignorant of the laws which control the distribution and localization of secondary neoplastic deposits. While it is known that most tumors designated as carcinomas produce metastases mainly by way of the lymphatics, and less often and less extensively by way

of the blood stream, there exist carcinomas which show a marked hematogenous spread (carcinomas of the thyroid, suprarenal, nevi, and chorionic tissue). Sarcomas metastasize more often by way of the blood channels than by way of the lymph vessels. Malignant tumors of the central nervous system usually remain within this organ system with their secondary deposits. The reasons for these differences in behaviour are unknown. There is no plausible explanation available for the tendency of certain organ tumors (carcinomas of the prostate, stomach, breast, and thyroid) to produce metastases in the bones, while carcinomas of the lung reveal the unusual tendency to localize in the brain. Muscle tissue and the heart are rarely sites of metastases. Inasmuch as metastases appear more or less frequently at the most unusual sites, without any apparent reason, it is evident, that it is extremely difficult to gauge the significance of a trauma on the localization of a metastatic growth.

From a medicolegal standpoint the existence of such a relationship is without significance in a given case, unless the particular metastasis is located in a vitally important organ and thereby hastens death, or may be considered as a precocial formation, as cancers are apt to produce normally metastatic growths. If reliable evidence can be advanced that such conditions prevail, a traumatic localization of a metastasis may be considered as the result of a compensable accident. The responsibility of the employer should be limited in such cases to the extent of the aggravation.

Although it appears to be only fair and just that in the granting of compensation awards a distinction should be made between cases in which the trauma appears to be the main causal agent, and those wherein the trauma arising out of work is a material aggravating factor acting upon and hastening the course of preexisting cancer, there exist laws in some countries in which this differentiation is not made (Moran). It is obvious that an undue and unequitable emphasis is placed upon the element of aggravation. In commenting on this fact, Moran stated, that this apparently regrettable failure of the law, not to distinguish between these fundamentally different classes of traumatic cancers, does not eliminate the fact that an intelligent differentiation fair for all parties concerned represents serious obstacles inherent in the insufficient knowledge as to the exact role an established trauma, sustained at a fixed area, may play in the subsequent development of a neoplastic process at the injured site.

2. PUBLIC HEALTH ASPECTS

The public health aspects of industrial cancers form a part of the problem of the cancer menace to the general population. It is worthwhile to recall that the tar and dye industry, which dates its origin back less than a century, is putting daily on the market new products, some of which possess cancer producing qualities. The industry, thus, affords a wide field for the action of these products, and, in fact, arranges the tables for a veritable nation-wide

experiment through industrial exposure, which, in turn, brings about a premature predisposition, usually acquired at a later age (Teutschlaender). The spread of cancer must be combated by destroying the evil effects of these noxae. This can be accomplished most effectively by an extension of industrial hygienic measures, as it is better and it seems to be much easier to prevent cancer of this genesis than to cure it. The proper appreciation of the urgency of the existing situation does not seem to be as general as is necessary and desirable even among medical men, supposedly sufficiently familiar with industrial medicine.

Thus, Selby recently asserted that cancer belongs to that group of diseases (appendicitis, cancer, pneumonia, anemia, and communicable diseases) that are of no industrial importance, except as causes of disablement. Apart from the fact that this investigator seems to be unaware that acute and chronic chemical pneumonia may result from an occupational exposure to nitrous oxide, sulfur dioxide fumes, and other noxious gases, and to various types of inorganic and organic dusts (silica, asbestos, iron oxide, and manganese), as well as that numerous forms of anemia are caused by an industrial contact with a great number and variety of industrially widely used chemicals (lead, mercury, arsenic, benzol, hydrazines, and organic solvents), the data presented show unequivocally and convincingly that cancer is a disease of remarkable, industrial importance, and that industry has a moral obligation concerning curtailment of the occupational hazards leading to cancerous disease.

It is unfortunate that most laws dealing with occupational diseases including cancer emphasize the compensation feature for disability sustained, and neglect the preventive aspect of these disorders (Allan; and Waters). In some states the law provides that the industrial commissioners and industrial boards are required to add to the industrial safety code such rules and regulations governing the installation, maintenance, and effective operation of safety measures in all industries and operations, as appear appropriate to prevent and combat certain hazards (Waters). In most instances such provisions deal mainly or exclusively with the control of dust hazards. It is evident that the industrial hazards giving rise to cancer require the introduction of much more detailed and extensive measures, than those considered in the ordinary provisions of preventive procedures incorporated in the industrial safety codes. The effective control of the neoplastic conditions in industry usually represents rather complicated and difficult engineering problems, in addition to the observations of elaborate sanitary and medical precautionary measures.

It seems to be essential for the introduction and enforcement of such measures, that through the cooperation of government and industry, a thorough study of the various operations with known or suspected occupational cancer hazards should be made in order to determine their extent and type as well as the peculiarities existing in the different operations under normal and abnormal circumstances, before an adequate and intelligent program of tech-

nical, sanitary, and medical precautionary and preventive measures is promulgated. Governmental factory inspectors should later on see to it, by regular and frequent visits to the factories, that the rules and provisions of the industrial safety code dealing with these conditions are put into operation and are strictly observed, and that negligence and willful violations of these provisions are punished as criminal offenses. Coroner's physicians and medical examiners should familiarize themselves to an increasing degree with the forensic aspects of industrial cancer, so that they can cooperate effectively and intelligently with public health officials and can fulfill their main function, that is, the prevention of wastage of human life in industry (Martland).

To counteract the complacency apparently shown by some manufacturers in this respect, which finds appropriate expression usually in the statement "we have no cases in our plants" (Flinn), an intensive educational campaign should be conducted among the managers of industrial establishments, so that they are made aware of their social obligations in regard to industrial cancerigenic health hazards. There is little prospect of an appreciable reduction in the number of cancer deaths from occupational causes or from other environmental agents, unless a more critical and searching attitude is developed toward these ailments, such as is exemplified in a statement of Colonel Smallman, cited by Henry: "Provided a fact and not a surmise is stated, however, inexplicable it may be at the moment, it will some day fit into the cancer picture puzzle in its right place at the appointed time. The introduction of preventive measures will be of more benefit to the future than to the present generation in industry, for it is now clear that even if the contact with the causal agent ceases, the disease unfortunately may manifest itself in years to come, provided the period of contact has already been sufficiently substantial. For consideration of preventive measures knowledge of the exposure period needed for subsequent manifestation of the neoplasm is important."

The occurrence of cancer cases in industrial establishments should represent an urgent indication for a thorough and intelligent investigation. The following facts should be ascertained (Henry): life history, work in factory, duration of trade, the duration of time which the substance suspected as etiologically important has existed in a trade, scrupulous care as to details of life history, sound knowledge of industry, follow-up of cases to the factory where patient worked, and study of industry or occupation, if necessary from its very onset, so as to be cognizant of the changes which are liable to occur in it, remembering that the introduction of a cancer producing agent into industry may not make itself felt for some 10 to 40 years and may leave its trace for 16 or possibly even 30 years after the cancer producing agent has been eliminated.

Since social and financial reasons require that the occurrence of industrial cancers is reduced as much as possible, public health laws should specify that not only all cases of industrial cancer from well established sources, but also all tumors in which only the suspicion of such an etiology exists are made

subject to obligatory notification to the public health agencies, by the employer and the attending physician, both being liable to punishment in case of failure to comply with the law. It would be desirable and advisable to extend this provision to all those industrial diseases, which can be considered as precancerous manifestations (tar and pitch warts, chronic tar dermatitis and melanosis, chronic roentgen- and radium-dermatitis, chronic radium osteitis, and papillomatosis of the bladder in dye and chemical workers), so as to gain some reliable information concerning the potential scope of the existing carcinogenic hazard. The law should also take cognizance of the fact that the development of industrial cancers may be delayed in individuals with precancerous conditions of industrial origin, and the incidence of recurrences in cured occupational tumor cases may be decreased appreciably and the ultimate prognosis greatly improved, if such workers are removed from any further contact with carcinogenic agents, not only of the same or related types which caused the neoplastic or preneoplastic disorder, but also of all those agents which may act upon the same organ or organs, which are affected (Mottram; Taschmer; and Gottlieb and Spitzer.)

Provision should be made by law that such workers are compelled to give up their hazardous work and receive an adequate allowance during the time they are under medical treatment and, after being cured, during the period they are trained in some other type of work, entailing no contact with the carcinogenic agents. Finally, the industrial use of carcinogenic agents should be regulated strictly by laws applying to the type of technical equipment used, the technical, sanitary, and medical precautionary and preventive measures to be taken, and the social supervision to be exercised over the workers exposed. It appears advisable that workers subjected to occupational carcinogenic hazards should be instructed to adjust their dietary habits in such a way, that adequate amounts of protective foodstuffs are consumed (vitamins and sulfur and calcium containing substances), and should receive, where indicated, the natural detoxicants (vitamin C, glucuronic acid, cystine, choline, calcium, and glycine) as special additions to their diet, so as to fortify, by such a protective and preventive medication, the natural agents of resistance, and forestall the danger of an exhaustion of these detoxicants in the body upon long continued and excessive exposure to carcinogenic factors.

The scientific basis for such a dietary management seems to be provided by the recent experimental investigations on the prevention of liver necrosis, hepatic cirrhosis, and carcinoma in rats which were fed a diet containing dimethylaminoazobenzene, as well as by related studies. Kensler, Sugiura, Young, Halter, and Rhoads reported the prevention of liver cancer in rats treated with this chemical through the addition of casein and riboflavin to the diet. Nakahara, Fujiwara, and Mori obtained a similar result by adding beef liver to the rat diet, while Ando claimed that yeast has an identical effect. György, Poling, and Goldblatt found that not only casein, but also cystine plus

choline prevent cirrhotic and carcinomatous liver lesions in rats, when added to their diet. Fieser maintained that it seems to be possible that cancer-producing hydrocarbons can be detoxified in the body by an interaction of disulfide compounds. Maisin, Pourbaix, and Van de Voorde noted that sodium glucuronate administered in the food or by injection to mice painted with benzpyrene reduced the incidence of the resulting cancers, and a similar effect was obtained when vitamin B_1 was fed to mice treated with the chemical carcinogen (Maisin, Pourbaix, and Camerman).

The problem of occupational neoplasia and numerous and various disease conditions which lead to it form a part of the problem of physical and mental national health on which depends, in the final analysis, the vital strength of a nation, its cultural and economical efficiency, and its existence as a self-respecting, independent, and valuable part in the community of nations. The care, preservation, and improvement of the health of the people as a whole represents one of the noblest and most important tasks of every genuine and honest government. Only that people is adequately equipped and prepared to face the unavoidable changes of fortune occurring in the life of every nation, and is able to withstand these perils with a firm confidence in its power, with an unshakable belief in its vital right of existence, and with an unquestioning conviction of its moral obligation of survival, that is sound in body, intellect, and soul. The fundamental requirements for a healthful living, not merely for a small, selected, and socially privileged group, but for the entirety of its citizens, must be safeguarded by suitable laws adequately enforced.

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THIS BOOK

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By W. C. HUEPER, M.D.

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