OCCUPATIONAL TUMORS AND ALLIED DISEASES

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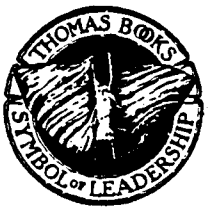

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This book **is** dedicated to the *memory* of those of our fellow *men who* have *died* from occupational diseases contracted while *making* better things for *an improved living* for **others.**

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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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, has 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

I. 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 bakeries. 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 Seen made repeatedly in connection with benzol poisoning of mild and proionged 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 tile 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 occurrente 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 detaii. 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 contac: 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 aleukemia, 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 fumesfrom 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 offidally 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; Liidke; 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 (Biingeler), 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, cardnogenic 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-