FILE NAME: Metropolitan Life (ML)

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NY Cancer Committee

in individuals first exposed afterwards. While the latter could have been unrelated to occupation in the regulated era, Smith acknowledged that people starting their employment in the 1930s "are only now reaching the mean age at which tumors might be expected to appear."[156,157]

In the published discussion of one of Smith's papers, Dr. A.J. Lanza offered this incredible critique of Merewether's data:[158]

> I think it is important to distinguish between cases of clinically recognizable and fatal lung cancer, on one hand, and cases in which the diagnosis of lung cancer has been made as more or less of an incidental finding at autopsy, on the other. The English claim for an association between lung cancer and asbestosis has been based, it seems to me, on data obtained from lungs that a pathologist has searched with a microscope. I wonder how many cases of lung cancer would be found if lungs from any sort of population were subjected to the same minute scrutiny?

Smith responded that the British Pneumoconiosis Board handled silicosis cases the same way as asbestosis cases, and so the silicotics could serve as a control group. In fact, the silicotics had an almost identical incidence of lung cancer as the general population, one tenth the incidence of lung cancer in asbestotics. In addition, many of the pathologists reporting excess lung cancer in asbestotics had done thousands of autopsies of the general population, and cited them as a comparison or "control" group. Further, no autopsy series of asbestotics was reported as having a "normal" rate of lung cancer.

Another person who commented after Dr. William Smith's report on European research on occupational cancer was Dr. Paul Cartier, of the Thetford Industrial Clinic in Quebec.[158] Cartier reported that his clinic had detected "eight cases of primary cancer of the lung" among an asbestos mine and mill working population of 4000. Other cases were suspected, but only those cases confirmed by an autopsy (or biopsy) were included. Of the eight cases described, two were called "pleural mesothelioma." The degree of concomitant asbestosis

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1014 N. Broadway, Cincinnati 2, Ohio,

January 20, 1958

Dr. Daniel C. Braun
Medical Director
Industrial Hygiene Foundation of America, Inc.
Mellon Institute,
4400 Fifth Avenue
Pittsburgh 13, Pennsylvania

Dear Dr. Braun:

Both Dr. Princi and I, having reviewed your paper, "An Epidemiological Study of Lung Cancer in Asbestos Miners" are pleased to accept it for publication in the AMA Archives of Industrial Health. We find the report not only of exceptional interest but a model of the epidemiologic method in diseases of the lung.

Our only criticism was that in pursuing the epidemiologic detail the paper became a trifle long and one got the impression toward the end that one had read this before.

I, myself, was particularly pleased to learn the main conclusion of the paper was against the association of lung cancer with asbestosis, for I had come to a similar conclusion on obviously far less information but was afraid to say so for this reason. I am enclosing a review which contains a few sentences that I have marked in this connection that appears in the Annual Review of Medicine, Volume 7, 1956. You will recall at this time evidence greatly favored the positive correlation of lung cancer on exposure to asbestos.

Sincerely yours,

Herbert E. Stokinger, Ph.D.
Acting Editor,
AMA Archives of Industrial Health

Enclosure

A review of what toxicologists and industrial hygienists are doing to develop threshold limits for concentrations of substances in the air, corresponding biological threshold limits, pretoxicosis tests, and prophylactic and antidotal agents . . . and a discussion of recent developments in the techniques of air sampling and air analysis.

Standards for Safeguarding the Health Of the Industrial Worker

By HERBERT E. STOKINGER, Ph.D.

THE EPITOMICAL STATEMENT made some years ago by Dr. James A. Sterner, now medical director of Eastman Kodak Co. and past president of the American Industrial Hygiene Association, announced a change of attitude among industrial hygienists which today is the keynote of enlightened occupational health practice: "No substance is so toxic that it cannot be used if sufficient knowledge of its action has been made available; similarly, no substance is so nontoxic that it should be used without regard to caution."

Currently, several effective means by which such a concept may be implemented are available: (*a*) threshold limits for concentrations of injurious agents in the workroom air, (*b*) threshold limits of concentrations of injurious agents or their metabolic products in biological fluids corresponding to the threshold limits for air (biological threshold limits), (*c*) tests of pretoxicosis to screen persons for early signs of injury from exposure to hazardous agents, and (*d*) prophylactic and antidotal agents.

Occupational hygiene standards in this country have been given various names, the most familiar of which is maximal allowable concentrations. Another designation is threshold limit values, the name used by the American Conference of Governmental Industrial Hygienists. Still another term is industrial hygiene standards, a designation recently adopted by the American Standards Association. All these terms refer essentially to the same concept of permissible contamination of workroom air by dusts, fumes, mists, vapors, or gases, although the bases on which the limits for certain substances are set may differ somewhat in the different lists. The following discussion will be confined chiefly to the list of threshold limit values, with which the author is most familiar. This list is prepared by the American Conference of Governmental Industrial Hygienists' Committee on Threshold Limits, which is composed of persons work-

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ing in State and local industrial hygiene departments and in Federal industrial hygiene units, and members of the armed services in the United States and Canada.

Only the United States and Russia appear to be currently developing such lists as the threshold limits list, other countries preferring to use those already developed. Partly because of this, but more especially because the abbreviated preface to the list only briefly refers to its application, the following paragraphs discuss in some detail the nature of the list and its purpose, methods by which the values are developed, and interpretation and proper usage of the values.

Nature and Purpose of the List

The threshold limits list includes those natural minerals and oils and chemical substances, including economic poisons but excluding radioactive materials, in the form of dust, fume, mist, vapor or gas, which are in sufficiently wide use industrially to warrant control of their concentration in the breathing zone of the industrial worker. (Permissible levels of exposure to radioactive materials are independently set by various radiation protection committees throughout the world. Values for many radioactive substances may be found in the National Bureau of Standards Handbook No. 52.) Because of the rapid development and application of certain chemical substances, often a timelag occurs between the industrial use of a substance and the appearance of the threshold limit value. This interval, however, is becoming shorter as a result of increasing attention of the chemical industries to the development of data on the toxicity and hazards of their products prior to use. Limiting values assigned to each substance in the list represent the maximal atmospheric concentration to which workers may be exposed repeatedly day after day without injury to health.

The purpose of the list is to provide a limiting value of air concentration for injurious substances for use by plant engineers, industrial hygienists, and others concerned with the health and comfort of the workers. The list is intended to be a guide for the control of working atmospheres and to provide management, labor unions, and the worker alike an assurance of healthful conditions on the job.

Development of Threshold Limits

A value for a toxic substance is assigned on the basis of data accumulated from animal inhalation toxicity studies and on the basis of industrial experience. Together, these represent, of course, ideal requirements not always fulfilled for each substance in the list but approximated as far as possible. Of the two, industrial experience is the test on which the validity of a value must ultimately rest. Because reliable information from industrial experience is frequently difficult to obtain, the Committee on Threshold Limits is often forced to rely on opinion of industrial hygienists, rather than on factual information, or sometimes, merely on animal data. Such opinions, however, are based on specific experience with various substances and come from occupational hygienists throughout the country. The current toxicological literature is also scanned continually for usable information. When the need for the assignment of a value seems urgent, a tentative value is assigned on the basis of the best information available at the time.

Originally, preventing impairment of health was virtually the only consideration in the selection of the proper limiting air concentration of an injurious substance. Now, however, with the increasing emphasis in occupational health on the "total man," more subtle effects on health, such as the effects of annoying or irritating agents, are also considered. Thus, whereas a threshold limit value of 3 or 4 p.p.m. for chlorine would insure no impairment of workers' health, this value is reduced to 1 p.p.m. in the interest of greater freedom from irritant effects. The levels of other gases and vapors with irritant or other discomforting effects on the workers have been similarly adjusted.

The rapid growth in the number and diversity of industrial substances to which workers are exposed and the increasing attention being given to occupational health in this country have given rise to a very real problem of maintaining the threshold limits list current. To meet this problem, the Committee on Threshold Limits reviews the lists annually, considering

carefully each value and any new information pertaining to a change in level. When a value is changed, it is so designated.

In the threshold limits list for 1954, a further accommodation has been made in an attempt to keep pace with the ever-increasing use of new industrial chemicals. This is the addition of a tentative list separated from the list of established values. Henceforth the tentative list will include all substances not previously listed. Because of the lesser certainty sometimes associated with these tentative values, they should provide only general guidance in the control of exposure and should carry no legal weight. The tentative list is looked upon as providing levels under trial and test, to be revised when new information justifies. Substances in the tentative list will not be incorporated in the main list until the values have been proved by experience to be acceptable. It is hoped that the tentative list will stimulate a greater number of yearly additions than in the past, as well as the critical evaluation of these values by greater numbers of industrial hygienists.

Overall Maximal Upper Limits

It is now considered desirable by a majority of the persons concerned with occupational health to assign a maximal upper limit of 1,000 p.p.m. for most, although not all, of the gases and vapors that are apparently nontoxic or nonhazardous. Such a limit has been set for certain Freons and other apparently innocuous substances, although it is known that neither health nor safety are endangered by exposure to far higher levels under ordinary conditions. In favor of this practice is the argument that it will prevent excessive or wanton exposure to air contaminants. It is recognized that all the facts needed to assure safety are seldom at hand. Physiologically inert substances, such as certain Freons and sulfur hexafluoride, in unlimited concentration may suddenly become hazardous, in the presence of welding or plumbing operations, through decomposition by heat to highly toxic products.

A similar concept is developing with respect to dusts that in the past have been considered essentially nonhazardous or not incapacitating. Numerous reports from various countries make it all too apparent that many dusts formerly considered inert are capable of producing pulmonary changes that are oftentimes disabling (*1–7*). It would therefore seem that all insoluble dusts of whatever nature should be held suspect until proved otherwise (*4*). Unfortunately, the assignment of a specific level for each mineral dust is impossible at present. Mineral dusts are commonly of complex and inconstant composition, often varying according to locality, and thus are potentially capable of causing a variety of physiological responses. As a case in point, pulmonary carcinoma is commonly associated with the long-term inhalation of asbestos in England, but not in America (*8*). Assignment of specific levels is also difficult because pulmonary changes derived from the inhalation of mineral dusts commonly require years to assess, because sound information relating exposure to response is not, for the most part, available, because exposures are not uniform owing to changes in the industrial process and job changes, and because dusts from operations involving the same materials often differ in size and surface area.

Therefore, it is believed that the validity of the present standards for dust should be reviewed and consideration given to the following suggestions. In the absence of information and in view of the poor prospect of obtaining any in the near future, the conclusion seems inescapable that if protection from dusts is to be guided by hygienic standards, an overall limit value should be selected. Actually, two values appear desirable, one for dusts containing free silica, and another for nonsiliceous dusts.

For silica-bearing dusts, a limit of from 2 to 5 million particles per cubic foot (m.p.p.c.f.) is suggested. It would be applicable to those substances containing free silica of any appreciable percentage (10 percent or more). Such a level appears justifiable on the basis of usage and experience, as shown in table 1, and tacitly assumes no other mineral is more hazardous than silica and/or any combination of a mineral with silica. Actually, this value represents a rather low level of exposure when

expressed in terms of milligrams of substance per cubic meter of air. Depending upon particle size, 5 m.p.p.c.f. silicon dioxide (SiO_2) with a density of 2.2 might range from 0.01 or 0.02 milligram to several milligrams per cubic foot, assuming the general size distribution of industrial dusts thus far recorded by optical methods (*9*); with dusts differing in density from SiO_2, corresponding differences in weight concentration, of course, would occur.

The question then arises of how best to express the dustiness of an atmosphere. Although this concerns matters too involved to be entered into here, it would seem that, with an absolute method now available for the measurement of industrial dusts, the limiting concentrations should be expressed in terms of either millions of particles per cubic foot or milligrams per cubic meter, or both, but within a definite size range, this range to be 0–3 μ diameter. Otherwise, dust counts, as well as expressions based on weight per volume of air, become meaningless. Particles of the size 3 μ and below can now be sampled and measured and are believed to be the only ones of hygienic significance. Whether the value approximating 5 m.p.p.c.f. will be found to hold when the submicroscopic particles are included is a very important project for future investigation.

Table 1. Recommended permissible limits of some silica-bearing dusts [1]

Industry or source	Reported percent free SiO_2 [2]	Recommended concentration m.p.p.c.f.
Sydney sandstone	90	[3] 6
Silica brick	80	2
Gold mining (Union of South Africa)	80	[4] 3
Granite	35	9-20
Pottery	30	4
Gold mining (Ontario, Canada)	25-35	[4] 8.5
Pyrophyllite	30-40	10
Anthracite (hard rock)	30	5-10
Nonferrous mines	20-40	5-10
Anthracite (haulageways)	13	10-15
Cement	6	20

[1] From a table prepared by Theodore F. Hatch, professor of industrial hygiene, University of Pittsburgh.
[2] Values are approximate.
[3] Owens Counter.
[4] Konimeter.

A practical threshold limit value for nonsiliceous dusts would appear to be 5 mg./m.[3] This value has been in satisfactory use for some years for controlling hematite dust and fume in at least one American plant (*10*). It would seem to represent a reasonable level of dustiness for all other presently considered "inert" nonsiliceous inorganic dusts.

More Specific Designations

With increasing industrial hygiene knowledge and experience, refinements in designating specific substances to which values are assigned will assuredly follow. As yet, however, only a beginning has been made in this respect. For chromium, the designation specifically refers to chromic acid or to chromates. The highly poisonous arsine gas has a threshold limit value of 0.05 p.p.m., whereas the value for arsenic and its compounds is 0.5 mg./m.[3] Differences in toxic action of uranium compounds have been recognized by individualizing the soluble and insoluble compounds.

It would appear that manganese dioxide would be a desirable designation for manganese, because manganese dioxide is the most common industrial hazard of this element. Mercury at 0.1 mg./m.[3] should refer to mercury vapor and its inorganic compounds and should not imply inclusion of the more toxic organic mercurials. Similarly, for fluorides the newer organic fluorides which vary widely in toxicity and hazard should be explicitly excluded, and for selenium, the threshold limit should apply only to selenium compounds which are highly toxic, not to elemental selenium dust, which is essentially nontoxic. The value of 0.1 mg./m.[3] for cadmium should refer specifically to the cadmium fume, for use of this limit for most of the insoluble cadmium compounds imposes far too severe a restriction. Different levels for lead and its compounds should be specifically defined according to information accumulated in the lead industries in this country over the past 10 years. Data show that whereas there is no reason to alter the value of 0.15 mg./m.[3] for lead fume or for lead dust of submicroscopic size, this value is unrealistically severe when applied to the more insoluble lead salts, and probably too lenient if applied to certain or-

ganic lead compounds. These and other desirable refinements in the list will undoubtedly be made in the near future.

Biological Threshold Limits

One new feature of occupational health standards that appears destined to play a useful role in evaluating personnel exposure in industry is what might be called biological threshold values, for want of a better term. These values refer at the present time to the greatest permissible content of an air contaminant or its metabolic derivatives in the body fluids, usually in blood or urine, although changes in other bodily constituents may in time serve also as measures of exposure. A list of biological threshold values, which correspond to the threshold limits for concentrations of the substances in air, is given in table 2. The values given for some of the substances are tentative, having been derived from limited experience; for others, such as lead and fluorine, the values are well founded. For still others, such as arsenic and mercury, there is considerable disagreement among industrial hygienists as to the usefulness of urinary determinations.

It is probable that the biological threshold limits of only a few selected substances will ultimately find an accepted place in occupational hygiene standards, since all substances are not amenable to accurate analysis in body fluids (complex organic molecules) by reason of wide individual variation in metabolism, interferences from dietary sources (arsenic), or simply the relative absence of constituents in easily obtainable body fluids (chromium, manganese, silver, and probably beryllium). For biological values to be serviceable, repeated determinations must be made on each person exposed, and preexposure control determinations are desirable. When biological threshold limits are used, they should supplement determinations of air concentrations, not replace them. In effect, these biological limits substitute diagnosis for the control or prevention of injury provided by air analysis.

Currently, in the lead industry, considerable enthusiasm is being expressed over the ap-

Table 2. Biological threshold limits [1]

Substance	Blood (mg./100 ml.)	Urine (mg./l.)
Inorganic constituents		
Arsenic		1 [2] (0.5 for arsine or lewisite).
Beryllium		0.002.
Cadmium		0.1.
Copper	0.1	
Chromium		Any detectable amount.
Lead	0.08	0.2.
Mercury		0.25. [3]
Manganese [4]		0.001.
Thorium		Not eliminated in chemically measurable amounts.
Vanadium		0.05. [5]
Uranium		0.01. [5]
Fluoride		4.
Selenium		0.07.
Tellurium		0.01.
Organic constituents		
Benzene		15 percent below normal sulfate ratio of inorganic to total sulfate.
Bromide	100	
Carbon disulfide		0.15.
Dinitro-o-cresol		5.
Methyl alcohol		5–7.
Methyl acetate		Analyzed as methyl alcohol.
Toluene (as hippuric acid).		3,000.
Trichloroethylene (as trichloracetic acid).		75.

[1] Many of the values given here are found in or have been revised from Chemistry of Industrial Toxicology by H. B. Elkins, New York City, Wiley, 1950, and in Analyses of Biological Materials as Indices of Exposure to Organic Solvents by Elkins, A. M. A. Arch. Indust. Hyg. and Occup. M. 9: 212–222, March 1954.

[2] H. H. Schrenk, in New Information on Arsenic Trioxide, Ind. Eng. Chem. 45: 11A (1953), states that urinary arsenic values of 4–5 mg./l. are commonly not associated with signs of arsenic poisoning. Use of urinary values is considered of doubtful worth because of great variation in normal values. Dietary arsenic, such as that obtained from seafoods, would greatly alter the urinary arsenic picture; moreover, arsenic is excreted chiefly in the feces.

[3] Urinary values may not always be reliable in long-term exposures owing to possibility of development of lower nephron nephrosis and for other reasons.

[4] Inasmuch as manganese is eliminated chiefly via the intestine, urinary determination is not a particularly valuable indicator of exposure.

[5] Tentative value.

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parently successful use of urinary lead values with or without prior screening by urinary coproporphyrin determinations. The argument in favor of the use of urinary values is that in practice most industrial exposures are neither uniform nor simple, but are mixed, and, therefore, that the body serves as a better sampling device and indicator of this type of exposure than do air samples. Biological determinations also offer a guide in the diagnosis of illness not provided by air analysis. Whether it is a wise decision to allow the individual to serve as his own indicator of exposure is debatable: Derangement of metabolic function or excretion for various causes is not uncommon among working populations, especially in older age groups, and concomitant exposure to other substances or other stresses may deflect normal metabolic pathways. It would appear reasonable, for the present at least, that biological values should be accompanied by one other independent method of evaluating the working environment.

Interpretation and Use

After the threshold limits have been accepted, it is most important that they be properly interpreted and used. Because there is some lack of agreement among industrial hygienists as to the use of the values, it might be worthwhile to consider what is meant by threshold limit or maximal allowable concentration. Confusion appears to center on the precise meaning of the term "threshold" or what constitutes "maximal allowable." These are brief terms used to express a rather complex and abstract concept which may be explained philosophically and operationally.

Philosophically, the threshold limit represents a level to which a normal healthy worker may be exposed for 8 hours each workday without harm to his physical or mental well-being. Because, in practice, most situations involve intermittent or varying exposures, the concept of the limit is that the summation of physiological effects of such exposures shall not be greater than the effect of exposure to a constant concentration at the level of the limit.

Operationally, the word limit refers to the highest permitted averaged values of an agent in the workroom air that have been obtained in a complete cycle of operations during the day. Proper averaging of concentrations should take into consideration the duration of exposure at each concentration; this is referred to as a "weighted average." Concentrations far above the limit for periods of 30 minutes or more and prevailing sporadically throughout the day, although possibly equaling the threshold limit, are not within the intended meaning of the term. Such levels come under the classification of acute, high exposures, and suitable measures should be taken to bring such levels in line with the accepted limit. Threshold limit values are not based on high, acute levels superimposed on a persistent lower level irrespective of what value their average is.

Threshold limit values should be used as guides in the control of health hazards and should not be regarded as fine lines between safe and dangerous concentrations, that is, a point above which injury is bound to occur and below which complete safety may be expected for all exposed persons. Competent judgment is required here as in the interpretation of any standard.

Misuse of Limits

The threshold limit values should be used only for control of exposure atmospheres for repeated 8-hour working days. They should not be used in the following ways:

1. For brief acute exposures. (The threshold limit values have been set on the basis of chronic exposures, not on the basis of brief acute exposures.)

2. For mixtures of substances. (There is no assurance that mixtures may not have potentiated and enhanced effects greater than the summated effects of each component.)

3. As levels for community air pollution or for levels to be derived therefrom by simple extrapolation. (The threshold limits have been set on the basis of an 8-hour exposure day with the assumption that a subsequent 16-hour period of nonexposure will aid distribution and elimination of the toxic agent from the body; therefore, they cannot apply to 24-hour continuous exposures common in air pollution conditions.)

4. As levels of permissible concentrations in community water supplies or for substances in solution. (Appropriate levels have been fixed specifically for several toxic elements in potable waters.)

5. As the basis for selecting dangerous compounds for labeling. (Hazards involved in handling chemicals frequently arise from routes other than inhalation, which is the basis for threshold limits.)

6. As safe limits for flight personnel in aviation. (Higher standards of safety and performance are required, and degree and duration of exposure at flight altitude differ from the degree and duration at sea level.)

Pretoxicosis Tests

Closely related to the biological threshold values are tests of pretoxicosis, the detection of subtle metabolic changes in the body before injury of serious proportions has developed. The idea is not new, the first reported test of this sort having been applied to the hematologic reactions of presaturnism by Heim de Balsac in 1908 (*11*). Although the determination of pretoxic reaction is unquestionably one of the highly desirable goals of the industrial toxicologist, few such tests have been developed mainly because the mechanism of action of most toxic agents on which such tests are based is not generally known.

A pretoxicosis test for carbon disulfide has been reported by Bourguignon (*12*). This test is based on the change in chronaxie, which, in turn, depends upon the knowledge of the vascular and neurologic changes caused by carbon disulfide during the early stages of injury. Chronaxie, by definition, is the minimal time that an electric current of standard strength is required for the excitation of the tissue. Bourguignon's report indicates that after men had been exposed to carbon disulfide for only 2 months and before any clinical signs of disease were manifest, their chronaxie changed. Accordingly, this test permitted early detection of intoxication by carbon disulfide.

Another test of pretoxicosis that is promising although it is still in the developmental stage is the lowered cystine content of fingernails of individuals exposed to vanadium. The lowered content occurs in the absence of any objective or subjective signs or symptoms in the workers, and it has been experimentally demonstrated in the hair of animals ingesting vanadium compounds in amounts that caused no demonstrable signs of toxicity (*13*). When used in combination with urinary vanadium determinations, the test appears to be highly suggestive of early metabolic changes resulting from exposure to vanadium.

The well-known urinary coproporphyrin III screening test for lead poisoning might well be classed as a pretoxicosis test. Used in combination with urinary lead values, it is now considered a reliable guide to incipient damage by lead (*14*). At potentially harmful body levels, lead is believed (*15*) to convert more of the normally occurring colorless precursor to the chromogen while increasing the total coproporphyrin of the urine.

The relative paucity of such procedures attests to the extreme difficulty of their development. Investigators should be encouraged to develop this aspect of preventive medicine, however, because its value obviously transcends that of diagnostic tests of established disease.

Prophylactic and Antidotal Agents

As the realization of the importance of toxicology in the development and safe use of industrial chemicals has widened, more diversified groups of scientists have become attracted to its problems. Such attraction has resulted in the development of a metal complexing agent, the calcium salt of ethylene diamine tetraacetic acid (CaEDTA), for the treatment of lead poisoning (*16*). This chelating agent has been given good evidence of effectiveness in numerous clinical trials (*17, 18*), and it gives promise of considerable versatility. It has been found, for example, to be a satisfactory antidote in experimental vanadium poisoning (*19*) and to give promise in the treatment of essential hypertension (*20*). Further use of CaEDTA for the more rapid elimination of other toxic metals having the capacity to complex firmly with this chelating agent at body pH conditions will undoubtedly be made. Since the advent of BAL (2, 3-Dimercaptopropanol) for combating arsenic poisoning, no

other organic complexing agent has proved of such value, although others, such as aurin tricarboxylic acid for the elimination of beryllium (*21*), have been suggested from time to time.

An ingenious and novel use of a complexing agent for combating cyanide poisoning has been recently reported (*22*). Cyanideless vitamin B_{12} (vitamin B_{12}", hydroxo-cobalamin) is capable of tightly coordinating with the cyanide ion in experimentally poisoned animals and thus preventing toxic symptoms and death.

Well-known reducing agents, such as ascorbic acid, have been reported experimentally at least to be effective prophylactically against a variety of toxic agents. For example, vitamin C was shown to function as effectively as CaEDTA against vanadium poisoning in animals (*19*), and this vitamin is reported (*23*) to reduce substantially fatal pulmonary edema and hemorrhage in animals inhaling ozone or nitrogen dioxide. Essentially complete protection against fatal ozone exposures in animals was afforded by a mixture of such reducing substances as glycuronate, cystine, and other similar substances that include vitamin C.

Two-carbon fragments administered as ethanol, acetate, and propanol have been reported to be capable of combating the highly toxic fluoracetate (1080) in animals (*24*), and they give promise of successful therapy for this poison. Cystine, methionine, and other sulfur-containing amino acids have been suggested as more general aids to the detoxifying capacity of the liver for protecting animals against the toxicity of 1,2-dichloroethane (*25*) and methyl-chloride (*26*).

Within the last few years, atropine has proved an effective antidote for parathion and other closely related organic phosphorous insecticides.

Air Sampling and Analysis

The development of valid threshold limit values goes hand in hand with the development of accurate procedures for sampling and analysis of the industrial atmospheric contaminants.

The Millipore Filter

Unquestionably, the greatest boon in recent years to such a development has been the introduction into the field of industrial hygiene of the Millipore filter (*27, 28*), known also as the membrane filter or molecular filter. This filter has an efficiency of sampling airborne particulates approaching 100 percent for all particle sizes of hygienic significance. The 150 μ thick paper of cellulose acetates and nitrates with 80 to 85 percent voids possesses a high dielectric constant and effectively attracts even noncharged particles of infinitely small size to its surface despite a mean pore size of 0.8 μ. Thus, the paper possesses a collection efficiency independent of the particle size of the aerosol. A limitation of the paper is that oils and tars clog the filter in a very short period of time, making it useless as a sampling medium for these materials.

Valuable use may be made of the property of the membrane to become transparent upon the addition of a limited amount of solvent (acetone, acetates, alcohols). This transparency permits the collected air sample to be directly counted under the optical microscope over a circumscribed, known area of the filter, thus providing a permanent dust mount that may be quantitatively analyzed.

Further advantage has been taken of the solubility characteristics of the Millipore filter by Fraser (*29*), who combined the high sampling efficiency of the paper and its solubility properties with electron microscopy to develop for the first time an absolute method of sampling and analyzing solid airborne particulates. In outline, the procedure consists of (*a*) collecting a sample of airborne particulates on the Millipore filter, (*b*) effecting transfer of the particles to a prepared electron microscope specimen screen after solution of the paper, (*c*) photographing the particles, and (*d*) determining the size distribution of the particles by visual measurement from their projection on a screen.

It is strongly urged that industrial hygienists take advantage of this powerful technique to explore the heretofore unsampled and unseen particles of industrial atmospheres and use such information to aid in the determination of their

industrial health significance. The results of such a study could well revise some of our concepts of the effective number of particles required to produce pneumoconiosis.

In the light of this and other recent developments, the Engineering Section of the Occupational Health Field Headquarters, Public Health Service, has undertaken an extensive reinvestigation of the entire field of dust sampling and measurement with the objective of developing improved generally acceptable methods that incorporate the advantages of these advances. Already the investigation has led to a promising use of the transparent properties of the Millipore filter, referred to above, as a dry, permanently fixed, dust sample for on-the-site use in plant or factory.

An automatic instrument which continuously records the mass concentration of dust in the atmosphere has recently been introduced (*30*). This instrument is based on the photoelectric measurement of forward-scattered light from solid or liquid aerosols and has a range from 10^{-3} to 10^{-2} μg./l. in terms of dioctyl phthalate as 0.3 μ diameter droplets. A further modification of this device is being undertaken by David Sinclair of the Johns-Manville Research Center in the development of an instrument which will indicate the size of the particulates as well as their concentration by electronically computing the ratio of backward and forward scattered light from the particles.

Another development in dust analysis techniques is the use of the electron microscope as an electron diffracting instrument. This technique is capable of exploring the surface of particles to the depth of approximately 0.05 μ in respect to their crystallinity or lack of it. In conjunction with X-ray diffraction techniques which determine similar properties within the core of the particle, it may provide much useful information concerning the relation between the physical structure of dust and its physiological effects. At the Occupational Health Field Headquarters, such work is being done on the various forms of diatomaceous earths, and in Scotland, on various types of silica (*31*). Efforts along this line are expected to go far in helping elucidate the etiology of various types of pneumoconiosis.

Vapors and Gases

Developments in sampling and analysis in the highly individualized field of vapors and gases during recent years have yielded no new principle or device, but rather they have found application for many of the methods long used in other fields. The study of air pollution has given a sudden impetus in this direction. Among the recent innovations used in the air pollution field are the portable Venturi scrubber (*32*), which has proved satisfactory for sampling ammonia, nitrogen oxides, aldehydes and sulfur dioxide, freeze-out trains, large-capacity plastic bags, silica gel, and other solid absorbents (*33*).

For the analysis of organic pollutants, the infrared analyzer and the mass spectrometer are being explored rather widely. Chromatographic procedures have also aided in the confirmation of many often closely related organic substances present in the air.

Automation appears to be the only really new basic development in this field in recent years. This principle has been most successfully applied to the measurement of sulfur dioxide in the form of the Thomas Autometer (*34*). This instrument is especially useful in situations where round-the-clock measurements are needed, or with further attachments for signaling added, it may be used successfully for control of gaseous concentrations. Automatic analyzers have also been developed for halogen analysis, for carbon monoxide (*35*), and for other substances. It should be emphasized that such automatic recorders in their present state of development require careful standardization and repeated attention and maintenance to assure faithful recording of actual concentrations. Commercially available recorders vary widely in this respect. If original design has been good and the instrument carefully standardized and maintained, the saving to industry over the years far outweighs the relatively high initial cost. Increasing automation is foreseen for the coming years in this and related fields of analysis and control of air concentrations of contaminants.

It may seem unfortunate that many of the recent developments in the industrial hygiene field often involve the use of equipment that is

expensive and nonportable. Immobility, but not expense, is fast being overcome when the need demands. A mobile infrared analyzer has been designed (*36*) and a portable mass spectrometer as well (*37*). High cost, a factor necessarily associated with increased complexity and sensitivity, will be slower to be overcome.

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Copies of the American Conference of Governmental Industrial Hygienists' list of threshold limit values may be obtained from Allan L. Coleman, chairman of the Committee on Threshold Limits, Connecticut State Department of Health, Hartford 6, Conn.

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Community Health Week, March 21–27

Community Health Week programs are recommended for March 21–27, 1955, by the United States Junior Chamber of Commerce in cooperation with the National Health Council.

Chapters of the Junior Chamber of Commerce have been asked by their national officers to name program chairmen for Community Health Week and to seek the aid of local health leaders. The program theme is "Know Your Community Health Resources."

Voluntary organizations are recommending that their affiliates provide the programs with cooperation and guidance. Basic health services will figure in programs where local public health units work with interested members of the organization.

Interested chapters will obtain a kit of aids from the national office. Suggested activities include health fairs and forums, special newspaper coverage, television and radio programs, exhibits, and school health projects.

Program leaders may wish to consult Guide to Health Organizations in the United States, 1951, by Joseph W. Mountin and Evelyn Flook. Public Health Service Publication No. 196. Available from the Superintendent of Documents, Washington 25, D. C. 30 cents.

TOXICOLOGIC ASPECTS OF OCCUPATIONAL HAZARDS[1]

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Within very recent years control of industrial hazards in the United States has become an integral part of plant operation. If the common industrial materials such as heavy metals and solvents still prove troublesome here and there, certainly it is the fault of application rather than the means of prevention, for these are now well defined in most instances. The accent is indeed on prevention; thoughts are being directed to tests of pretoxicosis rather than of injury. Considerations of comfort, rather than merely health, are being woven into the threshold limits of industrial exposure. The concept that the "total" man should be considered has brought into the fold many fields of study that have never gained consideration before. Toxicology has played no small role in the broadening of these concepts. Serious attention is being given to what were formerly fringe endeavors: psychology, psychiatry, effects of radiations, heat, light, vibration, noise, fatigue, color, and the design of machines fitted to the comfort of man. These enlarged and foresighted concepts have been recognized in the recent change of name from industrial health to occupational health, and have served to expand the realm of toxicologic activity. For the same reason, the number of fields that might be included in a review of this type is so large as not to permit the inclusion of all. Prominent among the topics omitted are discussions on occupational dermatoses, toxicology relating to pesticides, plastics, water quality, food, drugs and cosmetics, and methods of sampling and analyzing air-borne constituents.

A few volumes (1a) have been added to the toxicologic literature in the past two years: *Toxicology of Industrial Organic Solvents*, by E. Browning; *Aviation Toxicology*, by the Aero Medical Association; *The Halogenated Hydrocarbons, Their Toxicity and Potential Dangers*, by W. von Oettingen. A few limited reviews on toxicology have appeared within the year; the one by Goldblatt on "Research in Industrial Health in the Chemical Industry" (1b) expresses a decidedly English point of view. Also in England there appeared a critical review of experimental methods in determining chronic toxicity by Barnes & Denz (2). An incisive address by Seevers titled "Perspective vs. Caprice in Evaluating Toxicity of Chemicals in Man" (3) deserves attention. The Manufacturing Chemists' Assn., long a leader in the field of labeling dangerous chemicals, has published a third revision of its manual L-1, "Warning Labels;" New Jersey has recently developed a state code for labeling based on these recommendations. The Subcommittee on

[1] The survey of literature pertaining to this review was completed in July, 1955.

Toxicology of the National Research Council is planning to establish a toxicologic center where information may be obtained; presently, limited toxicologic information is obtainable from the Chemical Biological Coordination Center, Washington, D. C. The Threshold Limits Committee of the American Conference of Governmental Industrial Hygienists has been active in adding many new chemicals yearly to the original list. A series of Hygienic Guides on Hazardous Industrial Chemicals, useful for plant supervisors, is being prepared by the American Industrial Hygiene Association, and an Encyclopedia on Instrumentation for Industrial Hygiene has been compiled jointly by the Occupational Health Field Headquarters and The Institute of Industrial Health, University of Michigan.

Dust Diseases of the Lung

Although during the last few years reports have appeared on more than a score of rather unusual inorganic dusts that have caused pulmonary injury in workmen, major research emphasis has still been centered on a relative few, chiefly, on silica in its various forms and associated substances, coal, cement, slate, etc.; on asbestos, and, to a lesser degree, on beryllium and vanadium. In the United States in 1952, 528 deaths were recorded (4) from pulmonary tuberculosis associated with occupational diseases of the lung; pneumoconioses, including silicosis, amounted to 1423; similar figures for England reported by Merewether (5) showed 1300 died of pneumoconioses in 1951. Tuberculosis was not the sole disease associated with pneumoconiosis for 16 per cent of 300 workers dead of asbestosis over the years had primary lung cancer also. It is of more than passing interest that the higher rate of cancer in asbestos workers in England is not paralleled in the United States or in Canada, according to Lanza (6). The cause for this difference may lie in the type of asbestos; asbestos is a fibrous form of several different species of minerals, a point often disregarded.

A symposium held in Boston in October 1953 was devoted to occupational diseases of the lung, and laid chief emphasis on silicosis and asbestosis. The pathology of asbestosis (7) was presented, roentgenologic aspects of both diseases (8), clinical observations on asbestos workers (9), its differentiation from other pneumoconioses (10) and the functional abnormalities of industrial pulmonary fibrosis (11).

Current study of the fibrotic diseases of the lung related to occupation may be divided into three areas: (a) contributing factors; (b) mode of development of the silicotic nodule; (c) treatment. Because the literature is so voluminous, both here and abroad, on most of these areas, only the more generally informative reports have been selected.

In a review of factors now believed essential to the production of silicosis, Dautrebande (12) discusses, as important, particle size, amounts of free crystalline silica, the presence of associated dusts and fumes, and breathing patterns. Particles of 3 μ and below in diameter, with special attention to those of 1 μ size, are now generally considered the most injurious from evi-

gence based on human autopsy material and dust-settling characteristics. The electron microscope permits accurate visualization of particles below 1 μ not heretofore possible with light optical systems. Dautrebande, on review of much evidence, considers silicosis a probability if the number of particles is greater than 1.7 mp cu. ft.[a] in contrast to this opinion, the current limit believed safe in the United States is 5 mp/cu. ft. (13) as measured optically. Much evidence has now accumulated to indicate that the nature of the substances associated with silica and even extraneous substances may influence greatly the onset and nature of the ensuing silicosis, and especially the particular crystalline structure of the silica itself. King *et al.* (14) have presented evidence on intratracheally injected rats to indicate that, of the various crystalline forms, tridymite was most rapid in producing a tissue reaction, followed by cristobalite, quartz, and fused silica, in that order. The more rapid reaction of the crystalline forms has yet to be explained. In this connection a limited French report (15) on possible pneumoconiosis from silica of fossil origin (amorphous) confirmed the findings of many previous authors who have found no nodular silicosis from untreated diatomaceous earth. A study of the United States diatomite industry by the Public Health Service (16) in co-operation with state health departments of California, Nevada and Oregon, involving five plants and 869 workers, showed, in agreement with past findings, that only one of 25 employees who had worked more than five years exclusively exposed to amorphous silica in the quarry had diatomite pneumoconiosis, but 22 per cent of 286 employed more than five years and working in mills exposed to high temperature calcined, or fluxcalcined, diatomite, showed findings consistent with pneumoconiosis. Calcining diatomite with or without flux (sodium carbonate) converts the far less active variety to cristobalite, a crystalline form, which is believed responsible for the increased response. It was not possible to draw the conclusion that there were any differences in the response to fresh and salt water forms of diatomite.

There is increasing evidence that the onset of silicosis can be hastened by the inhalation of other substances along with silica. The alkalinity associated with sand in a scouring preparation was reported (17) to have caused silicosis in from 20 to 26 months ("galloping" silicosis) in a small group of exposed individuals; the silica dust concentration was tremendously high as far as can be gathered from the original report. Rapidly progressive silicosis has been previously reported in this country (18) from the same cause. Talcosis of unusually rapid development (16 to 24 months) was reported (19) also under circumstances of excessively high talc concentrations. Fluoride, in the form of fluorspar, in mixture with quartz has also been reported (20) experimentally to induce more intense fibrosis than quartz alone, although the latter may be present in only minute amounts (1 per cent) in the mixture.

[a] Million particles per cubic feet of air.

Isolated reports continue to appear with increasing frequency to incriminate many dusts, formerly considered inert, in the production of pneumoconiosis, such as sepiolite (21), corundum (22), feldspar (23), graphite (24), porcelain (25), barita (26), cement (27), mica (28), slate (29), kaolin (30, 31), and a substance to which gas workers are exposed (32).

Several reports in the last few years from the U. S. and England (33, 34, 35) are in agreement that coal miners' pneumoconiosis is an entity distinct from silicosis. Some unknown factor other than inhalation of coal dust, probably an infectious agent, is believed necessary, however, for the development of confluent lesions. The reports indicate a need for reinvestigation of the entire problem of soft coal mining (36). A study of the emotional aspects of respiratory diseases of coal miners has been made by Ross, Miller, Leet and Princi (37); psychoneurosis was the most significant diagnosis in one-third of 40 miners who had been referred to them for special study.

Mechanism.—The solubility theory (38) as an explanation for the formation of the silicotic nodule now appears to be weakening under more critical study. Almost as soon as it was enunciated, much evidence was produced that cast doubt that solubility alone could account for the development of the silicotic reaction. Among the first were experiments contrasting the reactions of the amorphous and crystal forms of silica, which show that highly soluble amorphous varieties were responsible for the toxic reaction, whereas the less soluble quartz produced the fibrogenic reaction (39). It is, of course, commonly known that the tissue reactions produced by amorphous and crystalline forms differ markedly, although the product of solution of each is the same, silicic acid. If silicic acid were solely responsible for the silicotic reaction, then silicosis should develop equally well from amorphous as from crystalline forms. Certainly, if solution of silica occurs, it must be either very limited in amount or localized in area, because no significant differences could be detected, with especially sensitive chemical methods, in the blood or in the urine of silicotics and of normals (40, 41, 42). Values in the urine varied with the acidity; no exact relation between blood and urine values was found, so that silica values could not be considered of either diagnostic or prognostic value. These facts have led to modified solubility theories. Experiments with silicic acid and proteins by Holt & Bowcott (43) showed, indeed, adsorption at the isoelectric points through amino groups chiefly. It had already been shown by German workers (44) that quartz particles become coated with serum constituents with no sign of dissolution, and Scheel *et al.* (45) have shown that the rate of solution of quartz is depressed by protein in such a way as to make it improbable that a simple solution of silica can account for its toxicity as manifested by silicosis. In a further study (46), these authors believed the toxicity may be due to a foreign protein reaction developed from the alteration caused by adsorption on quartz of normal serum proteins as shown by immunologic reactions. This important conclusion would appear to render less significant the opinions of Holt *et al.* (47) that the action of silicic acid in silicosis is a process

of aggregation and disaggregation, depending upon pH, which alters the permeability of tissue membranes. Holzapfel (48) likewise inclines toward the view of the combination of silica with tissue constituents, but has shown specific adsorption with a galactose complex; a galactan, containing only D-galactose, has been isolated from beef lung (49). Similarly, Heffernan (50) rejects the solubility theory, and propounds the surface-valency theory whereby freshly fractured silica surfaces fix large masses of organic material; asbestos acts similarly.

Whatever the final answers to the mechanism may be, the most convincing evidence now favors specific chemical combination of crystalline silica particles with certain tissue constituents, with consequent structural alteration from normal to produce local disturbance and typical silicotic response. Some crucial experiments are needed to confirm these views: (a) actual measurement of crystalline silica particles after many months' residence in the lungs, to determine whether solution occurs, (b) the demonstration that crystalline silica specifically combines with some pulmonary tissue component and can then produce the typical silicotic nodule.

Treatment.—The value of aluminum treatment, and especially the prevention of silicosis, after 10 years of trial, chiefly in Canada, is still open to final appraisal. Unfortunately, good control studies in man are almost nonexistent. Publications on the subject may be obtained from the McIntyre Research Foundation, Toronto, Canada. Dautrebande has proposed a treatment procedure, using a fine aerosol spray of sodium chloride to aggregate the silica particles (51). Animal experiments with this aerosol have shown excellent protective effects; whether field trials now in progress will prove the method of prophylactic value is yet to be reported. In Germany a recent form of treatment of silicosis (52) depends upon the use of electroaerosols consisting of unipolar mists of a calcium-sodium salt solution charged negatively and kept in suspension in an electric field before inhalation by the patients. Claims for effective treatment also have been made for an electroaerosol produced from sea water (53). Intermittent, positive-pressure breathing appears to be the most promising method of affording relief and control of symptoms in the majority of cases of emphysema and fibrosis with dyspnea according to Motley (54). Studies to assess the benefits of the method, however, were reported (55) to be complicated by the use of bronchodilator drugs. When this factor was tested, it was concluded that administration of oxygen and nebulized bronchodilators with improved breathing technics was, in most cases, as good as intermittent positive-pressure breathing.

Organic Dust.—The capacity of organic as well as inorganic dust to produce lung changes has been documented in several reports. *p*-Dichlorobenzene was reported to have produced pulmonary granulomatosis in a middle aged woman (56). Examination of excised lung tissue by polarized light revealed crystals believed to be *p*-DCB. The woman had been using *p*-DCB profusely for from 12 to 15 years on upholstery, carpets, and in clothes-cupboards as an insecticide. Caution has been voiced on the inhalation of resin

dust by Child & Clancy (57); during grinding and powdering of the synthetic resin, dryness of the mouth and nasal mucosa, coughing and sneezing, and other signs of respiratory irritation were in evidence. Experiments in animals produced wheezing, rales, blocking of major bronchi with distended resin granules, and salivation and atelectasis; the most prominent effects were caused from the loosely cross-linked resins. Dust and powder of Teflon (tetrafluoroethylene polymer) have been known for several years to produce a respiratory condition akin to metal-fume fever (58); more recent investigation of the inhalation hazards of heated Teflon (59) showed the evolution of highly toxic fluorine-containing decomposition products. "Printers' asthma" has been reported from England (60) to arise from inhaling a sprayed fluid containing gum acacia. Although considerable study has been given to cotton dust in relation to byssinosis (61), it is not yet clear which of the two structurally related components of cotton dust and associated mold are responsible for the "early" and "late" reactions. In bagassosis the endotoxin of *Aerobacter cloacae* had been proposed as a factor in its etiology (62). Pulmonary disability from the inhalation of grain dust is marked by dyspnea, chronic bronchitis, recurrent bronchial obstruction leading to clinically apparent emphysema, and was reported to occur among those working with seeds and grains for 10 or more years (63). This all-too-brief review of lung diseases from inhaled particulates makes it difficult to escape the conclusion that all dusts, irrespective of their nature, if breathed in sufficient quantity and for sufficient time, may cause profound damage to the lung, and emphasizes the desirability of the physician's obtaining an accurate and thorough occupational history on individuals suspected of pulmonary disease.

Beryllium.—A number of cases of both acute and chronic beryllium poisoning continue to appear, despite the fact that one of the major sources of exposure, beryllium phosphor in fluorescent lights, has been eliminated. In addition, an extremely low air standard of 2 μg.Be/m^3 for continued daily exposure, and no higher than 25 μg. for brief exposures, has long been suggested by the Atomic Energy Commission, one of the greatest users of beryllium. To our knowledge, no cases have appeared to date from the rigid use of these standards which have often been designed into production plants. Because of the peculiarly long latent period for the onset of beryllium disease, only time can tell whether the recommended figure for chronic exposure is a reliable one. The cases that arise are partly from exposures long past, but also partly from beryllium put to new uses such as glass, glazes, and alloys, and a certain number from beryllium production. Partly on the basis of the recent case incidence, Van Ordstrand (64), who was one of those who originally called attention to beryllium disease in the United States, has written of berylliosis as a real but preventable disease.

Diagnosis continues to be a difficult and controversial matter, however. Lieben & Jackson reported (65) that at least one case of their six, formerly diagnosed as berylliosis, was silicosis. Three new cases, two positively identified, one doubtful, have appeared in their factory since their earlier report

[illegible] have been suspected, but none conclusively demonstrated, according to Shilen *et al.* (66) in a study of beryllium extraction, reduction, and alloy fabrication covering a period of 10 years; beryllium concentration in the plant air through the years has ranged from a few micrograms to 600 $\mu g./m^3$. A summary survey of all clinical types of berylliosis observed in a 12-year period has been given by DeNardi *et al.* (67); a total of 431 patients were observed and treated for acute beryllium intoxication. Curtis (68) states that dermatitis due to beryllium is of an allergic-eczematous type, with the beryllium ion believed to be the sensitizing allergen. The patch test has been used with success in a limited number of cases as a diagnostic test of beryllium granuloma of the lung; a positive test was always found with true beryllium involvement, while negative results were obtained in Boeck's sarcoid and in normal beryllium workers. A registry to collect and correlate data on cases with beryllium poisoning is being accumulated by Dr. Harriet Hardy at the Massachusetts General Hospital, Boston. Work is continuing by Schubert and co-workers (69) on the mechanism of protection of aurin tricarboxylic acid in beryllium poisoning; ACTH treatment has provided no lasting beneficial effects, but Hardy (70) believes that either adrenocorticotrophin or cortisone is of real value in controlling symptoms though not in curing the disease.

Vanadium.—The study of vanadium compounds in relation to respiratory disease has been given serious attention since 1952 for two reasons: first, the mining and milling of unprecedented quantities of carnotite ore ($K_2O \cdot U_2O_3 \cdot V_2O_5 \cdot H_2O$) in this country in connection with securing uranium for atomic energy purposes has increased the number of exposed individuals; and second, the finding of respiratory illness among workers producing vanadium compounds for high-grade steel and other purposes, by Sjoberg (71) and by Roschin (72), as well as among workers cleaning boilers fired with vanadium-bearing oils, by Williams (73), Sjoberg (74), and by Fallentine & Frost (75), and from gas turbines [Browne (76)]. Sjoberg has written a monograph (77) in English on the health hazards in the production of vanadium pentoxide. The responses to air-borne vanadium dust are: slight irritation of the conjunctivae; slight or copious rhinitis, with acute or chronic hyperplastic changes in the nasal mucosa; dryness or irritation of the throat, with chronic atrophic, and sometimes also acute, changes; hoarseness; only mild acute changes in the mucous membrane of the larynx, and a cough as the most outstanding symptom, often with many rhonchi, although bronchoscopic examination shows only mild bronchitis. Pneumonia has been diagnosed in several cases and was considered to be of chemical-bacterial origin ("vanadium pneumonitis"). The responses are thus acute, not chronic, temporarily incapaciting, but not fatal. Dermatitis is not a common feature of vanadium exposure.

Experimental research on the systemic effects of vanadium compounds carried out in laboratories of the Occupational Health Program, United States Public Health Service, has shown that vanadium is capable of inducing at extremely low tissue concentrations (1 $\mu g/g$ of tissue) derange-

ments of basic metabolic processes which are not manifest clinically or felt by the worker. It has led to a highly sensitive test of pretoxicosis and to conclusions of practical value in the management of the health of vanadium workers. The critical feature of the pretoxicosis test is that the cystine content of the nails is depressed following chronic low-grade exposures to vanadium (78). Amounts of urinary vanadium resulting from exposure may amount to no more than 20 to 30 μg per l. when cystine depression occurs, according to a sensitive analytic method developed in these laboratories and reported by Talvitie & Wagner (79). Another important observation was that diet plays a deciding role in the toxic response. Complete, well-fortified diets have been shown experimentally to counteract the potentially toxic effects of vanadium, whereas borderline diets failed to do so, suggesting the value of nutritious and well-balanced diets for vanadium workers. The basic cause of the dietary differences has not yet been determined; metal antagonism, vitamins, or other factors may be responsible. Certainly vitamins exert a beneficial effect, for it has been shown (80) that ascorbic acid can counteract the effect of lethal doses of vanadium compounds in animals, if administered in small repeated doses within a short period after the fatal vanadium dose. Vanadium has also been shown capable, at nontoxic vanadium levels, of reducing elevated plasma cholesterol in rabbits fed high cholesterol diets (81). Reduction in arterial plaque formation was associated with this response. The significance of the role of vanadium in atherosclerosis requires further elaboration. Possibly the most interesting aspect of this entire research is that vanadium is merely one of a number of similar substances to which man is continually being exposed, through contaminated air, water and food, from which trivial amounts of materials may cause deep-seated metabolic alterations in the body.

Edathamil in Metal Poisoning

Poisonings from a variety of metals are still being reported, although the proportion of cases occurring in the United States in relation to worker exposure is decreasing; this does not appear to be the case in foreign countries. Of the metals, lead is now receiving renewed interest. The surge of interest arises for three reasons: (a) several cases of lead poisoning, some fatal, among children eating painted lead surfaces have been recognized in many of our larger United States cities; (*b*) a new and effective method of treatment has been found in a chelating agent, ethylene diamine tetraacetate, (EDTA) which has been given the generic name of Edathamil, by the Council on Pharmacy of the American Medical Association; (*c*) case of lead intoxication are still being seen in some smelting operations, brass foundries, auto-body shops, lead storage-battery plants, and printing establishments.

Reported cases of infant mortality from lead are as high as 30 per cent, increasing to 65 per cent when complicated by encephalopathy (82). Stimulated by facts like these, the American Standards Association has drawn up specifications to minimize hazards to children from residual surface-

coating materials; this activity was sponsored by the American Academy of Pediatrics. It is small wonder, therefore, that early reports of the effectiveness of EDTA in children (83, 84, 85) were recieved enthusiastically. The more recent excellent report of its use in adults by Sidbury (86) would seem to leave little doubt of the value of EDTA in lead poisoning. This report presents a review of the action of EDTA with reference to papers showing its distribution and excretion in man and in animals, dosage-schedules, and case reports with lead-excretion curves following therapy. The value of a chelating agent such as EDTA is its capacity to combine with metals so as to render them un-ionized. The combination often has reduced toxicity and allows an increased rate of excretion via the kidneys. EDTA is used as the calcium salt because this form eliminates the development of low-serum-calcium tetany. As with most drugs, there may be obvious dangers from prolonged, wanton or excessive use. Dudley *et al.* (87) have already described toxicologic changes associated with the use of EDTA in treating hypercalcemia: "At autopsy, unexpectedly severe damage occurred to the renal tubules with engorgement of the reticuloendothelial cells with gross eosinophilic granules and hemorrhagic manifestations." Kehoe (88) has considered as unwarranted the continued use of EDTA as a prophylactic measure for lead workers as a substitute for reduced lead air levels in the workroom. Preparations for such use would be orally administered where absorption has been shown to be minimal (89); hypotheses, and not proof, have been offered to explain EDTA's action by the oral route.

Edathamil has been experimentally tested in mice for its effectiveness in manganese poisoning (90): it prevented the disease from progressing, but did not reverse the serious effects of manganese on the nervous system. Edathamil has been reported (91) to accelerate the excretion of plutonium in man, especially directly after plutonium intake and "offers promise in a situation formerly considered hopeless." CaEDTA was reported (92) to decrease the excretion of mercury in a single case of combined mercury and lead exposure in which the patient was successively treated with dimercaprol and EDTA. Fatal doses of vanadium administered to experimental animals were successfully counteracted by later treatment with CaEDTA (93). Edathamil has also been shown experimentally to increase excretion of yttrium and americium (94) and zinc (95). CaEDTA, combined in an ointment, has been reported by Maloof (96) to be of value in the treatment of chronic ulcers; EDTA loosens and permits easier removal of the ulcer base in at most two or three applications. EDTA has also been recommended in the treatment of lime burns of the eye (97).

Solvents

The last few years have witnessed a gratifying trend generally in the approach to the development, marketing, and use of the safer solvent. The contact of industrial workers with solvents is probably the greatest of any single group of substances; their injurious effects range from extreme hazards

...ous and fatal injuries, to dermatitis. The awareness of the hazards of solvent use has greatly increased in recent years because of the increase in toxicologic information and education on the risks involved. This knowledge has served to curtail the use of many of the more hazardous solvents: the highly flammable solvent is now less commonly used without admixture with a nonflammable component; the seriously toxic benzene is restricted to limited and controlled uses, and the less hazardous toluene or xylene substituted for it; several safer chlorinated hydrocarbon solvents are now substituted for carbon tetrachloride. The hazards of carbon tetrachloride are considered so great that some companies have forbidden its use, or, if permitted, require experienced supervision, or usage limited to small quantities. Unauthorized or flagrant use still persists, however, as two recent excellent reviews testify (98, 99). Supportive treatment of severe CCl_4 intoxication now emphasizes, in addition to attention to the liver injury, the management of renal tubular damage with its possibilities of pulmonary edema and potassium intoxication. Death frequently results from the last. It is now clear also that many of the severe and fatal cases of poisoning involve chronic alcoholics or individuals who have ingested alcohol prior to, during, or after CCl_4 exposure. Despite the known potentiation of toxicity of halogenated hydrocarbons by alcohol, the chief approach to safer solvents is the use of chlorinated hydrocarbons of lesser toxicity than CCl_4, namely, trichloroethylene (TCE) (100), perchloroethylene (101) and, more recently, methyl chloroform (102); the threshold limit values for these agents are, respectively, 200, 200 and 500 p.p.m. in comparison with 25 p.p.m. for CCl_4. These threshold limits provide a rough indication that some hazard remains even with the use of these substitutes; indeed, cases of fatal exposure to TCE have been reported (103), but exposures were far in excess of the threshold limit, presumably several thousand p.p.m. Study is being given the excretion products of TCE, especially trichloroacetic acid (TCA) (104) as a measure of exposure, but the results and interpretations are complicated by the variability of the liver's capacity to metabolize the TCE. Some authors conclude that TCA cannot be used as a simple test of exposure to TCE (105). Another solvent, methylal (dimethoxymethane), of relatively low toxicity with a threshold limit approximating 1000 p.p.m. (106), appears to have received less attention and use, possibly because of its high volatility and flammability.

Other approaches have been made toward so-called "safety" solvents. One such approach is the use of the azeotropic mixture (107) whereby a constant b.p. for all components is achieved. This has the practical advantage that the vapor from the mixture has the same composition as the original mixture, thus permitting a more exact knowledge of the composition of the exposure vapors and preventing the disproportionate build-up of vapor concentrations of the more volatile substances. The use of solvent mixtures as a substitute for the single solvent is now common with all producers, the components of the mixture being selected for their nonflammability and lowered

toxicity. A typical solvent mixture now on the market is methylene chloride 25 per cent, perchloroethylene 5 per cent, and Stoddard Solvent 70 per cent, having a threshold limit approximating 500 p.p.m. Associated with the use of solvent mixtures is the question of the synergistic effect of the combination wherein the total toxicity may be greater than the sum of that of each component. Such effect is believed to occur from mixed exposures to methyl alcohol and methylene chloride, or carbon monoxide and many of the halogenated hydrocarbons, and there are others. LaBelle (108) has shown that particulate substances may enhance, decrease, or have no effect on the toxicity of a vapor, depending on its nature. The same worker (109) showed also that the toxicity of a solvent mixture of eight components was essentially that of its chief (55 per cent) component, methyl ethyl ketone. Likewise, McCollister (110), working with various fumigant mixtures of ethylene dichloride and dibromide and CCl_4, showed that the toxicity of the mixture could be mathematically predicted from the composition, i.e. no synergistic effect. Thus, whereas one should always be mindful of the possibility of synergistic effects of mixtures, synergism is by no means a necessary consequence of mixtures.

A new group of "OXO" solvents is now being marketed, so-called from the process that adds oxygen to unsaturated olefins to make a series of unsaturated aldehydes and alcohols that will have large application as paint and varnish solvents, components in safety glass, vitamin intermediates, and many other uses. Price margins in this field being small, and purification being costly, mixtures of these "OXO" solvents may be customary in the coming years.

A number of solvents are used as vaporizing liquids for fire extinguishers. CCl_4 is by far the most common and important; however, other halogenated hydrocarbons are being introduced as replacement for, or in combination with, CCl_4 (111). Of the newer agents chlorobromomethane has received the widest usage; the hazards of this liquid are somewhat less than that of CCl_4 (112), the main advantage in firefighting being that CH_2ClBr can be used at lower temperatures and is not as corrosive on metal extinguishers.

Air Pollution

The increasing importance of this subject to occupational health would appear to justify greater space than has been heretofore allotted it (113). Now, after six years of research and study and an overabundance of discussions and symposia, three major areas of accomplishment appear to have emerged. Much is now known of the nature and amounts of solid particulates contributing to the air pollution of many cities, both in the United States (114–118) and abroad (119). The total particulate load in the air over many United States cities ranged from 200 $\mu g/m^3$ in residential areas to 500 $\mu g/m^3$ in the air over industrial areas, of which identifiable metallic constituents accounted for from 5 to 10 per cent; the bulk of the remainder was carbonaceous material. Considerable uniformity of the particulate matter in the

...from city to city was found, and the more toxic elements, such as Pb, Mn, Cr, As, Be, etc. were invariably less than 1 $\mu g/m^3$ on the average, and although unquestionably contributing to over-all body burden, these levels were well below those usually considered hazardous. Recently, however, new importance has been attached to the water-soluble fraction of these particulates by Hemeon (120), to which he ascribes the capacity of respiratory irritation. In this connection, it should be noted that the particulates over cities with little or no industry were similar in nature and only somewhat smaller in amount than over areas with high industrialization (121). This is expected, as many elements (Ti, Mg, Si, Al, Fe, Ca, Pb, etc.) are common to soil, rock, cement, and paint that find their way into the air by attrition.

In the continuing search for evidence, that still proves elusive, of the long term effects of air pollutants on human health, a second possibly important area was developed in the demonstration, first in England (122, 123), and later in the United States (124), of atmospheric carcinogens; a large number of the commonly recognized polycyclic aromatic carcinogens have been identified in the atmosphere and in gasoline engine exhausts. Whether the amounts found in the general atmosphere (less than 1 $\mu g/m^3$) are sufficient to induce lung cancer in man is still to be demonstrated. They have been shown, however, capable of causing skin cancer in mice (124). Other types of air-borne carcinogens such as printing inks (125) have also been implicated as causing bronchial carcinoma (Stockholm); and rubber tire dust, also carcinogen-containing, has been found in appreciable quantities in the air of our largest city. Rather detailed inventories of automobile gases have been made (126), and the distribution of these gases in city air estimated (127). It is estimated that of the more than 2000 tons of total hydrocarbons evaporated into the air of Los Angeles each day, 440 tons are unsaturated hydrocarbons, of which 220 tons arise from autos and service stations, and the remainder from gasoline production: smoke particulates from auto exhausts are estimated at 50 tons per day.

The third major contribution to the understanding of air pollution is the demonstration of certain basic reactions of aerosols, by Haagen-Smit and co-workers (128), for Los Angeles air, namely that oxidants are the chief contributors to eye irritation and crop damage. Potential oxidants arise in the air from natural and man-made sources through a complex set of chemically and photochemically catalyzed reactions involving oxygen, nitrogen oxides, and hydrocarbons. Among the products detected, and they are numerous, ozone and oxygenated hydrocarbons (peroxides) are considered to be the serious offenders. More recently Haagen-Smit has demonstrated that ozone may be photochemically generated from auto exhaust gases (129). It has long been known (130) that combustion engines are capable of forming nitrogen oxides by fixing the nitrogen in the air and, like unburned hydrocarbons and ozone, the quantities formed depend upon operating variables (131). This, and related information (132), has provided speculation on the possibility of either better engine design for more complete burning of fuel,

or the use of selected types of fuel that will not yield oxidizable, potentially eye-irritating hydrocarbon derivatives in the exhaust.

It is hoped that a greater proportion of future research on air pollution will consist of the study of the basic reactions of aerosols (synthetic approach), for it is wholly possible that the conventional methods of sampling and analysis of the atmosphere will completely fail to detect or identify the more highly reactive and transitory types of pollutants that will prove ultimately to be the worst offenders. It is probable also that still more potent, elusive, and unusual types of air pollutants are yet to be discovered (133). By a combination of both approaches, however, greater assurance of obtaining the objectives will be had.

The question of the chronic effects on health is still awaiting development of tissue function tests specific enough to differentiate between the effects of air pollutants and those of tobacco smoke, infectious processes, aging, etc. Epidemiologic surveys are suitable for indicating the areas for investigation, but final proof that air pollutants cause injury to organ systems must rest on direct objective evidence from tests of functioning of the affected organ.

Ozone and Oxides of Nitrogen

Because ozone has an essentially "clean" odor, ozonizers are periodically recommended for their air-cleansing value in hospitals, homes, offices, and garages. Ozone also is found associated with many industrial activities, such as welding, electrostatic precipitators, or other electric-generating devices. Because of ozone's powerful oxidizing action it is now being used in the fine organic chemical industry, in water purification, and in cheese storage rooms. These uses have led to an increased number of potentially serious exposures to a substance long known for its toxicity. Moreover, the role of ozone in Los Angeles smog has lately assumed major proportions. Recently, however, a new note in the toxicity picture of ozone was injected by Thorp (134), who claimed that the oxides of nitrogen associated with ozone production were responsible for the observed toxicity. Refuting evidence was recorded by Weaver (135) in a brief review on ozone toxicity. Because of the danger that Thorp's statement could be misinterpreted and misapplied (and, indeed, such statements have found their way into recent toxicology texts (136), the present author undertook a review and study of the problem of the relation of oxides of nitrogen to ozone toxicity. The review (137) showed no convincing evidence to support the contention that the oxides of nitrogen would account for ozone toxicity, chiefly because, under usual circumstances of ozone generation, only small amounts (usually 1 or 2 per cent or less) of nitrogen oxides are produced. Animal studies (138) further showed that addition of oxides of nitrogen to ozone up to 50 per cent failed to alter the toxicity of ozone, the LD_{50} of which for mice approximated 4 p.p.m. for 6 hr. exposures. In support of these findings, Gray, in a series of studies (139) on the oxides of nitrogen (chiefly NO_2) produced from red fuming

were used, found the LD_{50} for rats to be approximately 75 p.p.m., and suggested the safe level for daily exposure for man to be 5 p.p.m.; this latter value has been incorporated into the threshold limits of the American Conference of Governmental Industrial Hygienists. The matter, however, appears still unsettled, for reports from England by Diggle & Gage (140) claim a toxicity for nitrogen pentoxide somewhat greater than that of ozone; the importance of N_2O_5 is that it is the product resulting from NO_2 in the presence of excess ozone. The experiments of Diggle & Gage were complicated by a variety of factors, and seem to this reviewer not to support the conclusions of the authors; certainly, more work must be done to attempt to resolve this controversial and difficult problem. Part of the difficulty has undoubtedly lain in the inadequate sampling and analysis procedures. To overcome these difficulties Byers *et al.* have critically evaluated and modified the method of Smith and Diamond (142) for ozone, and Saltzman (141) has developed a highly sensitive and accurate method of sampling and analyzing nitrogen dioxide. Other difficulties may also stem, as suggested elsewhere in this review, from varying conditions of humidity, or the presence of as yet undemonstrated free radicals of a highly toxic nature, and these may prove responsible for the differences in the present experimental conclusions.

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Occupational Diseases and Industrial Medicine

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Chapter 15

Occupational Cancer

There are many diverse forms of neoplastic growths constituting a group of disorders rather than a specific disease entity. Ewing, years ago, defined a neoplasm as an autonomous new growth of tissue. Cowdry offers this definition of cancer: "Cancer is a condition manifested by a wide variety of cells of the body from before birth to the point of death in more or less remote response to the action of hundreds of influences. . . ." The over-all incidence of cancer has been increasing steadily for more than a century. Despite tremendous amounts of study and research, the etiology of cancer remains a mystery. Such diverse agents as the various forms of ionizing radiations, ultraviolet light and a few chemicals ranging from complex organic structures to metallic salts can initiate the development of cancer in man.

Exposures to cancer-producing agents occur in many occupations and are not limited to manufacturing industries. The farmer, sailor and outdoor worker suffer a high incidence of skin cancer from exposure to the ultraviolet portion of sunlight. Within industry, there is exposure to chemical cancer-producing agents and to some types of ionizing radiations. Cancer-producing agents are called carcinogens. Most occupational cancers occur in the skin and the respiratory system, since they are directly exposed to the various carcinogenic agents (oils, waxes, coal tar, pitch, soot and asphalt). Inhalation of chromium dust, nickel dust and nickel carbonyl, coal tar fume, "isopropyl oil" vapors, and radioactive dusts and gases may cause cancer of the respiratory tract. In addition, inhalation and absorption of β-naphthylamine or benzidine dust or vapors cause cancers of the urinary bladder, the tissues affected being those undergoing the greatest intensity of exposure to the carcinogenic material.

Cancer does not appear at once upon exposure to a carcinogen nor among all individuals exposed. In general, it is believed that the greater the intensity of

the exposure and the more potent the carcinogen, the sooner cancer will develop. Apparently, once sufficient exposure has been incurred in a susceptible individual, discontinuing the exposure does not prevent the development of cancer. Workers who have been exposed a few or a number of years to a carcinogen and then changed jobs, have been known to develop cancer many years later. In the intervening years, no signs or symptoms appeared. Perhaps a microscopic cancer in situ existed for some time prior to the development of overt cancer, but such lesions never have been demonstrated in connection with an occupational exposure to a carcinogen.

As with all occupational diseases, occupational cancer is poorly reported. Ordinarily, the establishment of a specific case of cancer as occupational in origin is impossible until a carcinogenic substance has been identified in the work environment. Moreover, the occupational cancer has no specific identifying characteristics. The problem of skin cancer is particularly difficult because of its prevalence in the general population. Scrotal cancer and bladder cancer, developing in an employee who has been exposed to a carcinogen, readily are recorded as occupational because of the low incidence of these cancers in the general population.

In view of the inherent difficulties in establishing a diagnosis of an occupational cancer and the paucity of materials established as carcinogenic to men, it is not astonishing that the total recorded cases of occupational cancers is small. In 1954, Hueper collected all such cases. He has recorded 750 cases of occupational cancer in the United States. About half of these are bladder cancers from exposure to specific aromatic amines. Coal tar and pitch accounted for 110 skin cancers, chromates for 75 lung cancers and a few heavier petroleum oils for 70 skin cancers.

History

Although in 1531 Paracelsus noted the prevalence of a deadly lung disease among the Schneeberg miners, it is unlikely that he recognized it as cancer. Sir Percivel Pott, in 1775, identified and described the first recorded occupational cancer. His description of scrotal cancer from soot among chimney sweeps emphasized both severe prolonged exposure and the latent period. Eckardt (1939) has assembled the historical data on a world-wide basis in an interesting table including dates, reported agent, site and number of cases reported (Table 15.1).

Eckardt properly points out that the actual number of cases is undoubtedly much larger due to inadequate reporting and lack of recognition. Particularly in skin cancers is this true. We have not accepted arsenic, saltpeter, and asbestos as adequately proved carcinogens and believe that they probably act only as co-carcinogens.

Sheepherders in the Balkans and outdoor workers in Kashmir, who during the winter carry beneath their clothing, next to the skin, pots of coals to keep

*Table 15.1 Historical Data on Occupational Cancer**

YEAR	FIRST REPORTED BY	REPORTED AGENT OR PROCESS	SITE	PROBABLE TOTAL NUMBER OF CASES REPORTED TO DATE
1775	Pott	Soot	Scrotum	190
1822	Paris	Arsenic	Skin	<[illegible]
1875	Volkmann	Crude Wax from Coal	Skin	254
1876	Volkmann	Coal Tar	Skin	>3000
1876	Bell	Shale Oil	Skin	>200
1879	Harting & Hesse	Ionizing Radiation	Lung	>300
1894	Unna	Ultraviolet Radiation	Skin	Unknown
1895	Rehn	Aromatic Amines	Bladder	>1200
1898	Mackenzie	Creosote	Skin	20
1906	Frieben	X-rays	Skin	>125
1910	Wilson	Shale Oil and Mineral Oil Lubricants	Skin	2000
1911	Pfeil	Chromate Producing	Lung	140
1917	Leymann	Crude Anthracene (coal tar?)	Skin	20
1926	Prunes	Saltpeter	Skin	17
1929	Martland	Radium	Bone	9
1932	Grenfell	Nickel Refining	Lung & Sinuses	135
1935	Lynch & Smith	Asbestos Production with Asbestosis	Lung	59
1952	Weil et al.	Isopropyl Alcohol Manufacture	Sinuses	10

* By permission. From Industrial Carcinogens. Modern Monographs in Industrial Medicine. Grune & Stratton, New York, 1959.

warm, suffer chronic burns, and squamous cell carcinomas have developed in the skin of the abdomen and thighs. Whether the radiant heat and chronic burns alone are the etiologic factor, or whether materials, perhaps tars, from the smoldering coals, charcoal, or leaves may be the specific exciting factor is not known. In Kashmir, these are known as Kangri cancers, Kangri being the name given the pot used for carrying the coals. Radiant heat also is probably a cocarcinogen.

Experimental Work

Despite knowledge of the carcinogenic action of certain agents, the precise nature of occupational cancer remains as elusive as that of other cancers. Experimental work to determine the carcinogenic ability or potency of a material uti-

DISEASES

PROBABLE TOTAL NUMBER OF CASES REPORTED TO DATE
190
<25
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>200
>300
Unknown
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lizes animals that are known to be susceptible to cancer. The carcinogenic potency of a material ordinarily is greater with increased concentration. Certain solvents and other materials have been shown to hasten the action or increase the potency of carcinogens; these are called cocarcinogens.

It is not clearly understood just how carcinogens act upon cells to alter their type of growth to a malignant pattern. Attempts have been made to explain this change in terms of cellular metabolism. Moreover, it was hoped that a relationship between chemical structure and carcinogenic activity could be found. Neither of these theories has been proved. Carcinogenesis may be described as the process of conversion of a normal cell to a malignant one and its subsequent growth to a detectable tumor. However, whether tumors develop from a single cell or a number of cells that have undergone malignant transformation due to a common cause is unknown.

Of the thousands of chemicals tested in various animals, hundreds have proved to be carcinogenic. However, only a few of these are used in industry thus serving as possible occupational carcinogens. The experimental work has emphasized the necessity of repeated exposures and the relatively long latent period. Moreover, experiments have substantiated the belief that the tissue primarily affected is the one which has suffered the most prolonged contact with the carcinogens.

Materials absorbed into the body may be metabolized and a few metabolites have been demonstrated to be carcinogenic. Thus, β-naphthylamine is metabolized to 2-amino-1-naphthol that is eliminated rapidly by the kidneys. After administering β-naphthylamine, the ratio of 2-amino-1-naphthol found in the urine to that found in the blood serum is about 200:1. Dogs who readily develop bladder tumors from β naphthylamine metabolize 70 per cent of such material to 2-amino-1-naphthol, while rats who ordinarily do not develop bladder tumors from this chemical only metabolize 15 per cent of the material to the carcinogenic metabolite. From this and other work, the 2-amino-1-naphthol metabolite has been established as the carcinogenic agent. It produces cancer in the urinary tract because it is in contact with these tissues in the highest concentration for the longest period of time. These research findings have added significance because of the possibility of the body forming this metabolite from related chemicals.

Epidemiology

Cancer is more difficult to establish as occupational in origin than any other occupational disease. Silicosis, for example, does not occur in the adult population from non-work connected causes. All forms of cancer resulting from the occupational environment appear in the general adult population. In addition, as the average age of the working population increases, the incidence of "naturally occurring" cancer rises. A second factor which makes recognition of occupational cancers difficult is the long latent period or interval between exposure and the

development of overt cancer. In the intervening period of years, the worker may have changed jobs or the industrial processes may have been altered changing the exposure completely. The latent period in mule-spinner's cancer of the scrotum is exceptionally long. A study of 300 cases in Great Britain indicated that the interval between a mule-spinner's first day in a textile factory and the development of scrotal cancer varied between 16 and 63 years. Of these patients, 67 per cent were between 35 and 54 years of age. Because of low incidence in the general population, two types of cancer—scrotal and bladder and possibly a third, nasal sinus cancer—should be considered occupational in an industrial employee until proved otherwise.

Because of the difficulties in establishing the diagnosis of occupational cancer in a single case, group studies seeking an increased incidence of cancer in the work group constitute a fruitful approach. Unless it is excessive, an increased number of cancers in a population group ordinarily is not self-evident. Painstaking statistical studies of mortality by occupation usually are required to establish a specific type of cancer as occupational in origin. Hueper has expressed this well. "The demonstration of an occupational origin of cancers depends mainly on statistical evidence which often shows an excessive incidence of a certain type or types of cancer in a restricted group of workers . . . At present only the most potent and obvious cancers and carcinogens have been discovered while those of low incidence rate caused by carcinogens of low potency have not yet been recognized."

In the epidemiological method of study, the amount of cancer in the population under study is determined, and expressed as an incidence, prevalence, or mortality rate. Basic material for such statistical studies is obtained chiefly from public health or insurance company records. Such studies may indicate an incidence of cancer higher than expected in a population. Physicians may discover that an unusual amount of cancer prevails among a certain work group. Once this suspicion arises, immediate study of the medical records of that work group is imperative. Here is where good industrial medical records are most helpful while poor records, lacking in follow-up or final diagnoses, are practically useless. For details of the structure of epidemiological studies, the reader is referred to Eckardt's monograph, "Industrial Carcinogens," or a publication by the Council on Industrial Health of the American Medical Association entitled "Occupational Cancer," J.A.M.A., 166:2171, 1958. Both publications present excellent material on how to conduct epidemiological studies.

In this connection, Cramer's hypothesis makes interesting speculation. Cramer suggested that the susceptibility to cancer might be determined by intrinsic factors, perhaps genetic. The effect of environmental carcinogenic agents might be only to determine the site at which cancer would appear. However, the material collected in occupational cancer studies does not bear this out for, with an increase of occupational cancer occurring at a particular site, there should be less cancer of other sites and this does not appear to be the case.

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Occupational Carcinogens

There are three categories of carcinogenic materials to consider. First, the established occupational carcinogens that have been proved beyond doubt as causing occupational cancer. Second, materials that are suspected of causing occupational cancer but not proved. Third, materials in use in industry that have been established as carcinogens for some types of animal in the laboratory but which have not been implicated as producing occupational cancer in man. Agents falling into the first two categories are presented in Tables 15.2 and 15.3. Table 15.2 presents the generally accepted and established carcinogens and the sites characteristically affected.

*Table 15.2. Established Occupational Cancer Producing Agents, with Sites**

AGENT	TISSUE
4-Aminodiphenyl (xenylamine)	Bladder
Anthracene, crude	Skin
Asphalt	Skin
Benzidine and derivatives	Bladder, ureter, kidney
Chromates	Respiratory system
Creosote	Skin
	Lip
Ionizing radiation (all types)	Skin
	Lungs
	Blood forming organs
	Bone
	Eye
Isopropyl oil	Larynx and sinuses
Mineral oil, crude	Skin
Naphthylamine-beta	Bladder, ureter, kidney
Nickel and nickel carbonyl	Respiratory tract
Paraffin, crude	Skin
Pitch	Skin
Shale oil	Skin
Soot	Skin
Spindle oils, aromatic	Skin
Tar, coal	Lip
	Skin
Ultraviolet rays	Skin
	Eye
Wax, crude from coal	Skin

* Modified from Occupational Cancer, a Challenge to the Physician, New York State Occupational Cancer Committee.

*Table 15.3. Suspected Occupational Cancer Producing Agents, with Sites**

AGENT	TISSUE
Aromatic organic chemicals	Liver
Arsenic	Skin
	Liver
	Respiratory system
Asbestos	Lung
Benzol	Blood forming organs
Beryllium	Lung
Carbon black	Skin
Chlorinated hydrocarbons	Liver
Estrogens	Breast (male)
Isopropyl oil	Lung
Mineral oil, crude	Respiratory system
	Lip
Naphthylamine-alpha	Bladder, ureter, kidney
Pitch	Lip
	Bladder
Radiant heat	Skin
Sodium nitrate, crude	Skin
Tar, coal	Respiratory system
	Bladder
	Blood forming organs

* Modified from Occupational Cancer, a Challenge to the Physician. New York State Occupational Cancer Committee.

Table 15.3 presents those materials that have been suspected of producing occupational cancer but are in dispute or have not been proved as a specific carcinogen.

Several points should be noted concerning Tables 15.2 and 15.3. In Table 15.2, the potency of the established carcinogens is not indicated. Particularly among the oils is this important. For example, shale oil is a much more potent carcinogen than crude mineral oil. Also, despite the high incidence of mule-spinner's cancer of the scrotum in the textile industry in Great Britain, none has occurred in the United States. The difference in the carcinogenic property of the oil in use is the best explanation. In the United States, particularly since the studies of Braun and Truan, there is considerable conviction that asbestosis does not predispose to the development of lung cancer. Until further evidence is forthcoming, we have arbitrarily placed asbestos in the unproved or doubtful group and arsenic in the suspected group. Finally, some substances appear on both lists. This comes about because a substance may be a proved carcinogen for one site, skin for example, but not be established as a carcinogen for another site, such as the lung. Analine does not appear on either list since it now has been established that it is non-carcinogenic

despite reports to the contrary in the older literature. Some entries in Table 15.3 are probably only cocarcinogens.

Numerous materials have been established in the laboratory as carcinogens. Even potent ones in the laboratory, although appearing in some occupational environments have not been incriminated as causing occupational cancer in man; 3, 4-benzpyrene is one example. It is known to be present in the exhaust vapors of motor vehicles, yet no increased incidence of cancer among garage workers or other exposed groups has been demonstrated.

The U.S. Public Health Service has compiled and published a survey of materials tested for carcinogenic activity. The second edition appeared in 1951, P.H.S. Publication 149. The student desiring to look up any specific material is referred to this voluminous publication.

Chief Sites

As indicated earlier, the site of action of an occupational carcinogen is the tissue it reaches in greatest concentration for the longest period of time. In other words, it is the tissue suffering the greatest exposure. Thus it is not astonishing that, of the four major sites of occupational cancer, two—the skin and respiratory tract—are tissues of primary contact by carcinogens. The third site, the urinary tract, particularly the urinary bladder, is the body tissue most exposed when a carcinogenic material rapidly is removed from the blood by action of the kidneys. The fourth and last chief site, the hematopoietic system, is the site of origin of leukemia which is caused by various forms of ionising radiations and benzol.

Skin. Eckardt states that over 75 per cent of occupational cancers are of the skin, with coal tar and shale oil being the chief carcinogens. Fortunately, skin cancer lesions are readily apparent and therefore cures are more easily effected. Skin cancer of occupational origin is particularly poorly reported. It is believed that cases occuring among farmers and outdoor workers due to ultraviolet radiation are treated by busy practicioners but seldom reported. Occupational skin cancers are predominantly squamous cell carcinomas, having no distinguishing characteristics from non-occupational skin cancers. As might be expected, the exposed portions of the body—the head, neck, hands and arms—incur most such cancers. This results from direct contact with the carcinogenic materials or deposition of such vapors directly upon exposed skin surfaces.

Pigmentary changes in the skin have been reported from exposure to carcinogenic oils but are not believed to be a precancerous skin response. However, areas of skin hypertrophy and atrophy occuring on skin exposed to carcinogenic oils are associated with skin cancers. Skin cancers developing under such conditions are considered occupational. Unexposed portions of the body also are subject to skin cancer, particularly if the clothing becomes saturated with the carcinogenic material. Thus, oil soaked trousers convey the oil to the scrotum

provoking mule-spinner's type scrotal cancer. Generally the latent period in skin cancer is long. 20–40 years or longer, thus years of exposure ordinarily are requisite for the development of such cancers. In this connection, regular cleansing of the skin certainly must play a part in delaying or preventing the occurrence of skin cancer.

Several materials produce skin cancer and there are probably others that have not been identified. The presently accepted skin cancer agents include ultraviolet light; ionizing radiations, alpha, beta and gamma, coal tar, soot, pitch, creosote, crude anthracene, and crude waxes; shale oils and crude shale paraffin oils, petroleum products, lubricating oils, crude paraffin oils, fuel oils, tars, asphalts, pitch, and carbon black. The chief groups exposed to these agents are:

ULTRAVIOLET LIGHT. Farmers, ranchers, construction workers and especially outdoor workers are exposed, with greater risk in the south and at high elevations where the intensity of light is greater.

IONIZING RADIATIONS. These agents affect radiologists, dentists, veterinarians, chiropractors, x-ray technicians, and scientists and technicians in various nuclear energy industries.

COAL PRODUCTS. Work groups exposed to coal tar, pitch, soot, creosote or crude anthracene include workers engaged in handling these materials in:*

- Gas works
- Coke ovens
- Blast furnaces
- Tar distilleries
- Patent fuel manufactories
- Lens industry during polishing
- Building and allied trades
- Roofing felt preparation and handling
- Flooring materials
- Weatherproofing materials
- Sweeping roads
- Making of felt
- Briquette works
- Road building and repairing
- Coal-tar-pitch pipe making
- Battery making
- Cord making
- Paint making
- Electrical equipment works, making cables, carbon brushes, carbon electrodes and insulation
- Work of seamen and fishermen
- Creosote or tar preservation of wood
- Working with impermeable paper and cardboard
- Caulking of ships

SHALE PRODUCTS. Work groups engaged in the production of shale oils and shale paraffin oils, European mule-spinners, machinists and others who worked continuously with shale oils. Little or no shale oil presently is being produced in this country and it appears that little is being used in American industry.

PETROLEUM PRODUCTS. Those exposed to these agents are workers engaged in the primary production and refining of petroleum products, as well as

* Table modified from Coal Tar and Cutaneous Carcinogenesis in Industry, F. C. Combes, Charles C Thomas, 1954.

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mule-spinners, gunsmiths, paraffin pressmen, and a large number of varied metal and tool industrial workers.

THE CARCINOGENIC FACTORS. The precise mode of action of ultraviolet light in the production of cutaneous cancer is unknown. The same is true of ionizing radiation. However, in both instances, intensity and duration of exposure are important. Also, absorption of these forms of energy by the basal proliferating layer of the skin cells appears to be necessary. In coal products, carcinogenic properties are found chiefly in the heavy oils and anthracene oil. Pure anthracene itself is not carcinogenic but 1, 2-benzanthracene and 3, 4-benzpyrene are among several identified carcinogens in coal-tar and coal heavy oils. Coal products are the richest sources of carcinogenic agents yet discovered.

The carcinogens in petroleum products are closely related carcinogens to the benzanthracene and benzpyrene found in coal products, the benzenoid hydrocarbons. Petroleum oils vary greatly in their carcinogenic ability depending upon the source, with shale oils being the more potent. Arranged in order of carcinogenic potency, depending upon their source are oils from: Venezuela, Borneo, Rumania, Persia, California, Mexico, Mid-continent, Texas, Pennsylvania and Russia. Refined oils are the least carcinogenic and the sulfonated oils used as detergents are harmless. Pure mineral oil and vegetable oils are innocuous. In the United States, carcinogens are not found in the mineral oil fraction of lubricating or cutting oils. The chlorinated hydrocarbon present in lubricating and cutting oils can cause a folliculitis but never produces cancer.

SUSPECTED SKIN CARCINOGENS. These include arsenic, sodium nitrate (saltpeter), radiant heat, chemical and physical trauma.

Among those exposed to arsenic are workers engaged in mining and refining ores containing arsenic and workers engaged in the production of and working with arsenic alloys. Nursery and agriculture workers using arsenical insecticides also are exposed.

Arsenical skin cancers are exceedingly rare, if they exist. Such a diagnosis would depend upon:

1. History of prolonged exposure
2. Characteristic arsenical skin manifestations.
3. Demonstration of arsenic in the skin, hair and urine.

It is the firm belief of those who have studied the evidence carefully that arsenic acts essentially as a cocarcinogen but is not in itself carcinogenic.

An excessive rate of skin cancer has been reported among the sodium nitrate or saltpeter workers in Chile. However, it is believed by many that this high rate likely is due to some factor other than the sodium nitrate, possibly ultraviolet radiation. Radiation heat, chemical and physical traumas are not carcinogens, at the most they act only as cocarcinogens.

Respiratory Tract Cancers. Soluble gases and particulate matter from inhaled air are deposited in the thin film of fluid covering the respiratory tract. With continuous respiration, these materials accumulate on the walls of the re-

spiratory tract from the nose to the terminal alveoli. Should carcinogenic material be present in the air, it is easy to see how the respiratory tract tissues would suffer the greatest exposure both in duration and intensity.

IONIZING RADIATION. The first occupational respiratory tract cancers occurred among miners in the now famous Schneeberg and Joachimsthal mines. First arsenic, then cobalt, were blamed for the excessive incidence of lung cancer but now it is agreed that ionizing radiation from both radioactive dust and gases (radon) were the carcinogenic agents. It is of interest that these mines provided the ore from which the Curies isolated radium. It is believed that between 40 and 70 per cent of the miners died of lung cancer. Neither the daily nor the total dosage of ionizing radiation received by these miners can be calculated at this time because of the great change in working conditions and ventilation of the mines. Radon gas is short lived but its daughters are radioactive. The amounts of radioactive gases and dusts present in these mines over the centuries are unknown. Mines producing radioactive ores in the United States usually have some radon gas and curiously enough some mines producing non-radioactive ores also have been found to have radon gas. As yet, uranium miners in this country, Canada and Africa have not shown any evidence of increased incidence of lung cancer. Nevertheless, a long term study of the uranium miners in western United States and the levels of ionizing radiation in the mines is being conducted by the Public Health Service.

In the production of lung cancer from ionizing radiations, great hazard from inhalation of radioactive dust is possible because of the accumulation, deposition, storage and long retention of dust particles in the lung.

CHROMATES. Machle and Gregorius, by an epidemiological study in 1948, first established the increased incidence of lung cancer among workers engaged in the manufacture of chromates. The Public Health Service study of seven chromate plants indicated that about 22 per cent of the deaths among chromate workers were caused by cancer of the lung. The mortality from other types of cancer was about the expected amount. It is estimated that the number of lung cancer deaths among the chromate workers was about 30 times that expected in the general population. Detailed study of the work environment in the chromate plants has not identified a specific form of chromium as the agent. Dr. Anna Baetjer has engaged in much laboratory experimental work with animals using chromates, but has failed to produce lung cancer. Hueper has produced bone sarcomas in rats by intrafemoral injection of calcium chromate. Following analysis of the environmental studies in the chromate plants, the carcinogenic form of chromium causing lung cancer is believed to be an acid soluble, water insoluble compound and probably trivalent. The carcinogenic form of chromium does not appear to exist in the original ore so the mining of chromium and its handling until the refining process is started bears no known risk of lung cancer. Also, machining and working with the finished elemental chromium are not attended by a risk of lung cancer, for pure metallic chromium is non-carcinogenic.

NICKEL. First from Great Britain, and more recently from Norway, have come reports and convincing studies implicating nickel as a respiratory tract carcinogen. The evidence for its being the agent responsible for cancer of the nasal sinuses is overwhelming. Also, the evidence indicates with certainty that it is a lung cancer carcinogen. Study of the work population in a Mond process plant has shown that the groups suffering the greatest exposure are those engaged in calcining the ore and those engaged in the extraction process using sulfuric acid upon the calcined material. In years past, much dust was produced and good dust suppressive measures were not used. However, the gas nickel carbonyl produced in the Mond process of refining nickel originally was believed to be the only carcinogenic agent. Recently five cases of lung cancer have been reported from a small Norwegian nickel refinery utilizing an electrolytic process, not the Mond process, and so not producing nickel carbonyl. Thus the risk of cancer is not confined to nickel carbonyl but is probably inherent in both solid and gaseous forms of nickel. Prolonged inhalation experiments with animals have produced adenomatoid changes in the lungs of rats and guinea pigs but no carcinomas.

"ISOPROPYL OIL." In the manufacture of isopropyl alcohol using concentrated sulfuric acid, small amounts of impurities called "isopropyl oil" are formed. As this process was used originally, four cases of cancer of the sinuses, one cancer of the larynx and one cancer of the lung occurred in the work group. With a change in process, "isopropyl oil" is not formed and no further cases of cancer have occurred. Experimentally, "isopropyl oil" has produced skin cancers and there is no doubt that it produces sinus and larynx cancer. Perhaps it is capable of producing lung cancer but this remains to be established. Among the chief constituents of "isopropyl oil" are isopropyl sulfates, isopropyl ethers, and some polypropylenes. Precise chemical identification of the carcinogen has not been accomplished.

COAL TAR. Lung cancer arising from industrial contact with coal tar has occurred with certainty only among coal gas workers. Generally, only workers employed in the retort house, having extensive prolonged exposure to the vapors and fume, have developed lung cancer. These cases have occurred when workers suffered direct exposure to the fume while working over or about the old style horizontal retorts. Operation of the modern type retorts may or may not be attended with some risk of lung cancer. It will take time and detailed investigations to settle this problem.

SUSPECTED RESPIRATORY TRACT CARCINOGENS. As with skin, arsenic must be listed as a possible carcinogen. However, from the evidence, this is true only when the individual has been grossly overexposed to inorganic arsenic for a long period of time and exhibits gross chronic arsenicism. Probably such an exposure could occur only when working with inorganic arsenical materials with little or no effort to control the arsenical dust in the work atmosphere.

Three cases of lung cancer associated with pulmonary berylliosis have been reported. Also, Vorwald has produced carcinomas in rats following the inhalation

of beryllium. Although beryllium may be a carcinogen, evidence that it is the agent producing lung cancer in man is lacking. As a precautionary measure beryllium dust should be carefully removed from the work atmosphere.

Urinary Bladder Cancer. As previously pointed out, beta-naphthylamine and benzidine produce cancer of the bladder. Alpha-naphthylamine is suspected of this, but it has not been proved. Aniline definitely does not produce bladder tumors and should be cleared of this implication. Beta-naphthylamine is metabolized in the body to 2-amino-1-naphthol and has been indicted as the carcinogen. Less clear is the carcinogenicity of the metabolite of benzidine, but perhaps 4, 4-diamino-3-diphenyl hydrogen sulphate is the culprit. The uncertainty arises because benzidine is a much less potent cancer producing agent, and the carcinogenic metabolite probably produced in much smaller quantity. One other compound, xenylamine, or 4-aminodiphenyl, has proved to be a potent agent in producing bladder cancer. Studies of its metabolite excreted in the urine indicates the presence of 4-aminodiphenyl and 4-amino-3-diphenyl hydrogen sulphate, which later increases in quantity and hydrolyzes to 3-hydroxy-4-aminodiphenyl. Thus the orthohydroxy amine conjugates have been isolated in high concentrations as urinary metabolites from bladder cancer agents beta-naphthylamine and 4-aminodiphenyl. A much weaker bladder cancer agent, the orthohydroxy metabolite of benzidine, is present in the urine in a lower concentration.

Work Groups Exposed. In places where the primary aromatic amines beta-naphthylamine, benzidine, xenylamine, and perhaps alpha-naphthylamine are used, workers run the risk of developing bladder tumors. The men actually engaged in handling these materials are most exposed when scraping or cleaning filters, or when materials being worked produce dusts or vapors. In modern plants with built-in protection, perhaps the maintenance men constitute the most exposed group.

Workers employed in the manufacture of basic dyes, the manufacture of some rubber anti-oxidants where alpha-naphthylamine or xenylamine are used in the process, and where benzidine is used to harden rubber, may be exposed to bladder cancer agents. Adequate protection should be provided for textile workers and employees in the printing industry where alpha-naphthylamine and benzidine are used. Beta-naphthylamine also has been demonstrated in small amounts in coal tar from gas works, and so workers in this industry should be adequately protected.

Prevention. Good engineering control of dusts and vapors, the use of closed systems, and observance of meticulous personal hygiene are required. Estimations of the amount of free amine in the urine have been reported as useful in checking the adequacy of protective measures.

The Hematopoietic System. Ionizing radiations, particularly gamma or x-rays and benzol, are the agents most incriminated in the production of occupational leukemias. Whether these agents are true carcinogens or merely act as co-carcinogens is unknown.

IONIZING RADIATION. The action of various forms of ionizing radiation is discussed in Chapter 20. It is sufficient to state here that occupational exposure to gamma and x-rays occurs in the nuclear energy industry, hospitals, medical clinics, physicians' offices, research laboratories, and in some industries where x-ray is used to detect flaws in metal castings or to examine a variety of other materials. All workers with these agents should observe adequate precautions and not be careless or indifferent concerning personal exposure. In many industries, the equipment is installed in such a manner that when in operation a worker cannot be exposed.

The incidence of leukemia among radiologists has been reported as high and there is experimental evidence to support such reports. Leukemia has been produced in mice by x-rays, with small repeated doses being more effective than larger exposures over a shorter period.

The use of radioactive isotopes emitting gamma rays in industry (particularly Cobalt^{60}, Iridium^{192}, Cerium^{137}, and Thulium^{170}) has been increasing. In some places, gamma radiography is replacing x-rays as a means of examining castings, forgings, etc., and no doubt will find increased uses in industry. Such materials are well guarded and shielded and so far no cases of leukemia associated with the industrial uses of radioactive isotopes have been reported. Although radium and thorium have considerable use in industry, cases of leukemia in those working with these substances have not been reported. As yet, these materials have not been indicted as the causative agents of occupational leukemia.

BENZOL (BENZENE). The many industrial uses of benzol as a solvent are discussed in Chapter 11. There its depressant effects upon the hematopoietic system are presented, but not its production of leukemia. The gradual transformation of the bone marrow from aplasia to hyperplasia has been reported. Also, leukocytosis has been reported as a transitory finding in the early stages of benzol intoxication. The varied peripheral blood findings in benzene workers have been referred to as the "leukemoid condition." This reaction is only one of many bone marrow reactions to benzol intoxication. Among such reactions are complete aplasia, aplasia with leukemoid reaction, acute leukosis without peripheral leukocytosis, and finally acute leukemia. All forms of acute and chronic leukemia have been observed among workers suffering from benzol intoxication. However, the acute or subacute myeloid types of leukemia appear to dominate. Vigliani has suggested that perhaps many cases of aplastic anemia actually were aleukemic leukemias.

As stated in Chapter 11, we are not inclined to give credence to the reports of long delayed cases of benzol intoxication developing even years after the exposure to benzol has ceased. However, it seems possible that leukemia might develop at some time after a prolonged exposure to benzol had ceased.

SUMMARY

Thousands of chemicals have been examined as to their carcinogenic powers and this information is contained in the previously mentioned Public Health

Service publication. Numerous materials established as, or suspected of being, carcinogenic agents are used in industry, yet today it is astonishing how seldom we see a true occupational cancer. This can be attributed to the institution of strict controls, chiefly engineering, through closed systems, ventilation, personal protective devices, and others, which serve to prevent exposure. As more workers in the older age groups continue to work in industry, more cases of so-called "naturally" occurring cancer will be found among these older employees.

At this time it is believed that we have established as carcinogens only the more potent of these agents. Moreover, it is known that marked variation exists between individuals as to cancer susceptibility. Theoretically, the weaker carcinogens should be able to produce cancer only in the more susceptible individuals. Awareness of all these facts makes it clear that detecting the weak carcinogens is next to impossible solely upon a clinical basis. Studies to establish a weak carcinogen of necessity must be of the epidemiological-statistical type embracing large groups of people who have been exposed for long periods of time. Although these studies are arduous, they are needed to clarify the status of doubtful or disputed cancer-causing agents, and to uncover presently unknown environmental carcinogens.

We should recognize the woefully weak and inadequate status of our present knowledge of cancer etiology and the means by which carcinogens produce cancer. It appears certain that some or many materials we now accept as carcinogens are in reality only cocarcinogens. However, this makes little difference. If, as a result of its presence in the work environment, workers develop cancer, such a material must be entirely eliminated from the work environment. If it is continued in use, it must be so completely controlled that no worker may be expected to develop cancer.

The possibility of a non-carcinogenic material being metabolized in the body and a carcinogenic metabolite being produced always must be recognized. Also, the long latent period is characteristic of weak carcinogens. Particularly in cancer of the internal organs are these factors of importance. Every physician should be alert to the possibility of occupational cancer arising from new materials nor now suspected of being carcinogenic.

Finally, we would be remiss in closing this chapter without making a plea for the keeping of full medical records on all employees, not only as to diseases diagnosed within the industrial clinic, but on all cases diagnosed and treated outside, thus making complete medical records available for all employees. Such records are indispensible when work groups are under study for an occupational disease, particularly cancer.

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