SECTION VIII

Posterity may know we have not loosely through silence permitted things to pass away as in a dream.

—Richard Hooker

CHEMICAL CARCINOGENS

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Recogniton of the causative role that chemicals in the workplace play in carcinogenesis dates back to 1775 when Percival Pott, a London surgeon, linked a high prevalence of scrotal cancer in young chimney sweepers to their occupational exposure to soot produced by the coal burned in the chimneys they cleaned. Today, over 200 years after Dr. Pott's discovery, workers in the United States and other industrialized countries are exposed to a multitude of chemicals, many of which are recognized as, or suspected to be, carcinogens.

Carcinogenic effects of chemicals in man are difficult to document because 1) cancers are generally not clinically evident until a lapse of up to 20 to 30 years after the first exposure has occurred and 2) chemical exposures in many workplaces are so complex that it is difficult to pinpoint the specific causal agent or agents and the concentrations of the agents primarily responsible for the ultimate carcinogenic effect manifested decades later.

For example, workers occupationally exposed to coke oven emissions are at increased risk of developing lung and kidney cancer. Yet, in spite of lengthy research and the evidence as related to cancer, all the specific carcinogens in the chemically complex coke oven exposures responsible for the increased carcinogenic risks have not been determined.

LEVEL OF EXPOSURE

There is considerable debate among scientists regarding the level of exposure to a given carcinogen required to cause cancer. It is beyond the scope of this chapter to review all of the arguments offered as to whether or not a threshold exists for chemical carcinogenesis.

We have currently no established scientific method to determine threshold levels for chemical carcinogens, if indeed such thresholds do exist. Moreover, if a threshold for a given chemical carcinogen were to exist, it would not necessarily be determinative of a safe exposure since in the industrial environment workers may be exposed to multiple carcinogenic agents which may compete for the same target site.

Multiple exposures can occur on the job, in the diet, and in the ambient and home environments. Under these circumstances, some people may have already received doses from multiple exposures in excess of any presumed threshold for any single carcinogenic chemical. Consequently, any incremental increased exposure to chemical carcinogens could then result in an increased risk of cancer, especially if this incremental exposure may already be in the area where the slope of the

dose-response curve has steepened (1). As a result, the National Institute for Occupational Safety and Health (NIOSH) has taken the position that it is not currently possible to demonstrate safe levels of exposure to all chemical carcinogens (2).

RECOGNITION OF HAZARDS

Carcinogenic hazards may be identified by epidemiologic studies of people who have been exposed to suspect chemical agents and by experiments in animals exposed to controlled amounts of chemical agents. In the workplace, the primary route of exposure is through inhalation although concomitant ingestion and skin contact can also be important. Consequently, inhalation exposure experiments in animals constitute the most relevant toxicologic approach for simulating the most prevalent exposure conditions in the workplace.

In assessing the evidence for cancer, be it from animal or epidemiologic data, one must consider the strengths and weaknesses of the individual studies as well as the consistency of evidence between studies. There are, however, no universally accepted criteria for the quality or the consistency of the data that are required before considering that a given chemical represents a carcinogenic hazard to man.

EPIDEMIOLOGIC STUDIES

Identification of carcinogenic hazards from epidemiologic data generally involves the use of cohort studies; that is, tracing the present and future mortality experience of groups of individuals exposed to a common chemical agent at or during a specific time period and comparing their mortality experience with a matched group not so exposed during the same time period.

Most frequently chosen as a control group in these studies is a group from the general population matched for age, sex, and race. By comparing the mortality experiences among the exposed and nonexposed control populations, it is possible to ascertain if exposure has increased the risk of a given cause of death. In this type of study, the calculation of a standardized mortality ratio (SMR) in order to compare the frequency of death from a given cause or causes in the exposed population with that in the control populations is extremely informative. An index of more than 1.0 indicates that an excess risk may exist in the exposed population. In such comparisons, however, because the working population may in general be healthier than the general population, an apparently less risky SMR of 0.90 to 1.0 on a specific cause of death may actually indicate an increased risk among those who have been exposed — the so-called "healthy worker effect."

As noted, the usual latent period or lapse time for development of chemically-induced cancer is about 20 years. Consequently, a mortality study which does not include an adequate proportion of workers with

long latent or lapse times following onset of exposure may yield erroneous conclusions as to the lack of health effects of those chemicals in the work environment that are being studied.

ANIMAL STUDIES

In epidemiologic studies, once a chemical or exposure condition has been shown to cause cancer, preventive measures may not be adequate to protect those who have had previous exposures, but who have not lived long enough for effects to be expressed in terms of clinical illness. A major advantage of experimental animal studies is the possibility of detecting a chemical cancer hazard earlier than if one waited for epidemiologic evidence of cancer in man to become available. Under such circumstances, preventive action can be taken much sooner.

To date, there are a number of instances in which data on cancer in experimental animals have been used to establish occupational health regulations in the United States. It is increasingly evident that experiments in animals can be important indicators of cancer risk for man. Almost all chemicals shown to be carcinogenic in man by epidemiologic studies have also been shown to be carcinogenic in appropriate animal models. Although this does not necessarily mean that a positive test for cancer in animals provides incontrovertible evidence of cancer risk for man, it does indicate that the chemical should be considered at least as a potential carcinogen for man.

Experts frequently recommend testing chemicals in more than one animal species, primarily to avoid false negative results. Nevertheless, this should not be interpreted to mean that, before a chemical can be called a carcinogen, it must be positive in two or more species tested. Naturally, however, the greater the number of studies that show that certain chemicals produce cancer in different species of laboratory animals, the greater the confidence in the conclusion that those substances pose a carcinogenic threat to man.

POTENTIAL OCCUPATIONAL EXPOSURES

The boundaries of potential occupational exposures to chemical carcinogens are ever expanding. The following occupations are some of those subject to recent investigations.

- Asbestos workers
- Auto repairmen
- Bakery workers
- Clothing pressers
- Coke oven workers
- Dairy industry workers
- Dental laboratory technicians
- Electricians
- Leather workers
- Photoengravers
- Roofers
- Rubber workers
- Vinyl chloride workers

Table 4 presents a list of occupational chemicals and substances which cause, or are suspected of causing, cancer and the target organ or tissue. It should be emphasized that this list is substantially incomplete in that many, if not most, chemicals in the workplace have not been adequately tested for their carcinogenic potential. As such, however, the format of Table 4 attempts to organize a growing body of data in a manner that may be useful for physicians in making a differential diagnosis of the possible occupational etiology of cancer cases in individuals. Additionally, this list may lead physicians and other health professionals to become more aware of the magnitude of the growing problem of chemical carcinogens in the workplace. Since occupational carcinogens may effect virtually all organ systems, physicians should be alert to investigate situations where clinically evident cancer could be associated with on-the-job chemical exposures.

One helpful data source for physicians is the registry of suspected carcinogens maintained by NIOSH as a subfile of the Registry of Toxic Effects of Chemical Substances (3). This Registry contains approximately 1,500 suspect carcinogens, most of which have not been adequately tested. Their inclusion on this list does not represent a process of substantive evaluation with respect to the adequacy of scientific data related to carcinogenicity. Rather, this list is a useful starting point to ascertain the extent of data regarding carcinogenic responses for a given compound. Even with these caveats, it should be evident that a number of compounds in this list may be shown to be carcinogenic in man following more detailed evaluation.

Observations by alert physicians and alert workers have frequently helped to identify problems of carcinogenic risk in the workplace long before they might otherwise be realized. Examples of this are hepatic angiosarcoma, a rare liver cancer caused by occupational exposure to vinyl chloride, and leukemia among workers in the manufacture of styrene-butadiene rubber. A number of other occupational chemicals have been shown to produce "marker" or unusual forms of cancer, such as the pleural and peritoneal mesotheliomas due to asbestos, and hepatic angiosarcoma due to inorganic arsenic. It is likely that careful follow-up of rare cancers or unusually high incidences of common cancers may help to uncover unsuspected chemical cancer hazards among other worker populations.

Unsuspected occupational cancer problems might also be predicted on the basis of structural similarity with certain chemicals and substances already shown to cause cancer in humans or animals. For example, Table 5 lists compounds that by virtue of their structural similarity to vinyl chloride would be suspected of posing possible carcinogenic risks to man. Surveillance by alert physicians of workers exposed to these substances might help to early identify potential future problems. Similarly, it is most important for clinicians to be aware of newer data on carcinogenesis emerging from experimental studies on animals. For example, preliminary data have indicated that trichloroethylene produces liver cancer in experimental animals (4), and data from Russia have suggested a human carcinogenic lung and skin response to chloroprene (5).

Table 4. Confirmed and suspected occupational carcinogens by target organ.

Target Organ/Tissue	Occupational Carcinogen: Confirmed	Occupational Carcinogen: Suspected
Bone		Beryllium
Brain	Vinyl Chloride	
Gastroenteric Tract	Asbestos	
Hematopoietic Tissue (leukemia)	Benzene Styrene Butadiene and other Rubber Manufacture Substances	
Kidney	Coke Oven Emissions	Lead
Larynx	Asbestos, Chromium	
Liver	Vinyl Chloride	Aldrin Carbon Tetrachloride Chloroform DDT Dieldrin Heptachlor PCB's Trichloroethylene
Lung	Arsenic Asbestos Bis (chloromethyl) ether Chloromethyl methyl ether Chromates Coke Oven Emissions Mustard Gas Nickel Soots and Tars Uranium Vinyl Chloride	Beryllium Cadmium Chloroprene Lead
Lymphatic Tissue		Arsenic Benzene
Nasal Cavity	Chromium, Isopropyl Oil, Nickel, Wood Dusts	
Pancreas		Benzidine PCB's
Pleural Cavity	Asbestos	
Prostate		Cadmium
Scrotum	Soots and Tars	
Skin	Arsenic Coke Oven Emissions Cutting Oils Soots and Tars	Chloroprene
Urinary Bladder	4-Aminobiphenyl Benzidine B-Naphthylamine	Auramine 4-Nitrodiphenyl Magenta

Table 5. Suspected carcinogens based upon structural similarity to vinyl chloride.

Suspected Carcinogen	Structure
Vinyl Chloride	$H_2C=CH$ Cl
Bromoprene	$H_2C=CHCH_2Br$
Chloroprene	$H_2C=CHCH_2Cl$
Epibromohydrin	$H_2C-CH-CH_2Br$ $\diagdown O \diagup$
Epichlorohydrin	$H_2C-CH-CH_2Cl$ $\diagdown O \diagup$
Perbromoethylene	$Br_2C=CBr_2$
Perchloroethylene	$Cl_2C=CCl_2$
Tribromoethylene	$Br_2C=CH$ Br
Trichloroethylene	$Cl_2C=CH$ Cl
Styrene (Vinyl Benzene)	$H_2C=CH$ $\hexagon$
Vinyl Bromide	$H_2C=CH$ Br
Vinylidene Bromide	$H_2C=C\,Br$ Br
Vinylidene Chloride	$H_2C=C\,Cl$ Cl

IN VITRO SCREENING TESTS

In vitro screening techniques have been developed which have promise for identifying chemicals with potential for causing cancer (6). These techniques are based upon a number of end points such as mutations and inhibition of DNA repair mechanisms. Such tests are done on a number of cell systems, including human cell cultures and bacteria.

Preliminary evidence reveals that nearly 90 percent of chemicals established to be carcinogens by animal or human data give positive test results in one or more of these in vitro test systems(7) It is not known what proportion of chemicals selected at random without prior knowledge as to their carcinogenic activity will give a positive result in these tests. Strictly speaking these tests *per se* do not indicate carcinogenic activity. Nevertheless, they offer considerable promise in the identification of those chemical agents which should be tested for carcinogenicity. Thus, the practicing physician needs to know about these test procedures and results, because they may give important clues as to the existence of potentially carcinogenic chemicals.

INFORMATION SOURCES

Well over one thousand chemicals have shown at least one positive test result for carcinogenicity. These chemicals are in Suspected Carcinogens, A Subfile of the Toxic Substances List (3), published in 1975 by NIOSH and updated periodically. The International Agency on Research on Cancer has also published a series of monographs which review the carcinogenicity of a large number of chemicals (8). The National Cancer Institute (NCI) currently has approximately 300 chemicals on long-term test for cancer in animals and much new information will become available over the next several years.

Both NIOSH and NCI maintain systems which issue bulletins giving summarized, recent information on the carcinogenicity of chemicals. Copies of the bulletins may be obtained from these agencies. They are intended to make more people aware of new research information on chemicals and cancer so that appropriate medical and other precautions and action can be taken to monitor and prevent undue exposure. Additionally, such bulletins will likely lead to new research studies to clarify the existence and magnitude of suspected carcinogenic risks.

Occupational health physicians must be aware of these data sources. The information they provide on cancer risk may provide the clues which would facilitate the physicians' recognition of corroborative evidence based upon their own clinical experience. Such evidence would in turn help to stimulate adequate control actions to minimize future occupational and environmental exposure to these chemicals.

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SECTION IX

It may happen that the physician will be asked what to do in a department where all known mechanical devices for the prevention of poisonous dusts and vapors have been applied, and yet, because of the very nature of the process, there is still contamination of the air. . . .With newer poisons, it may be that the physician will have to study for himself the physiological effects in order to discover what sign or symptom can be depended on to give the needed warning of danger. . . .let me beg the industrial physician not to let the atmosphere of the factory befog his view of his special problem. His duty is to the producer, [worker], not to the product.

—Alice Hamilton

PESTICIDES *

Wesley E. Straub

This section deals with a discrete group of chemicals that are of particular importance in agriculture, pest control industries, and public health. Their use in crop production and disease control has increased with the expanding world population, and their complexity and number have increased in proportion to their expanded use.

No attempt is made to present the clinical effects of all pesticides currently in use nor to delineate definitive treatment. Some aspects of clinical treatment are presented, particularly where the information is of general application to more than one substance and is not generally available, and treatment must be rapidly instituted. Hazardous exposures may occur in both occupational and nonoccupational activities, and the physician should be on notice to consider both aspects of a worker's activities in checking for source of exposure.

In severe poisoning, the initial diagnosis and institution of appropriate treatment must be made on clinical grounds alone since there is generally insufficient time to wait for confirmatory laboratory results.

Essential to the correct diagnosis of pesticide poisoning is a high index of suspicion on the part of the physician based on 1) a history of opportunity for any adequate exposure compatible with time-dose relationships, 2) clinical manifestations, and 3) laboratory confirmation.

The toxic dose and clinical picture of poisoning vary with the compound and formulation, and possibly with the individual.

For purposes of the following discussion, the pesticides are grouped according to their chemical nature or use as organophosphates, carbamates, chlorinated hydrocarbons, bipyridyls, coumarins and indandiones, rodenticides, fungicides, herbicides, fumigants, and miscellaneous insecticides.

ORGANOPHOSPHATES

The more important organophosphates are:

Abate	Ethion
DDVP (Vapona)	Fenthion (Baytex)
Diazinon	Gardona
Dicathon	Malathion
Dimethoate (Cygon)	Naled (Dibrom)
Dursban	Parathion
EPN	

The organophosphate insecticides are characterized by the similarity of their mechanism of toxic action. They differ widely, however, in inherent toxicity and, to some extent, in rate of absorption and excretion.

The organophosphates act as irreversible inhibitors of the enzyme

*Based in some parts on the Chapter in the previous edition written by Roy L. Gibson, M.D., and Thomas H. Milby, M.D.

cholinesterase, thereby allowing the accumulation of acetylcholine at nerve endings. They are rapidly absorbed into the body by ingestion, through the intact skin, including the eye (even more efficiently through cuts, abrasions, areas of dermatitis, etc.), and by inhalation.

Dose and dose-interval affect the speed with which the toxic manifestations occur. Onset of symptoms more than 12 hours after the termination of exposure generally excludes the diagnosis of organophosphate poisoning. It must be remembered, however, that continuing exposure may occur from contaminated hair, shoes, and clothing.

The following table for parathion lists symptoms which are indicative not only for parathion, but for other organophosphate exposures.

Table 6. Signs and symptoms in patients with parathion poisoning as related to levels of cholinesterase activity.

Sign or symptoms	Total number of patients with signs or symptoms	Number of symptomatic patients in each of three levels of activity*		
		0-10% of normal	11-20% of normal	21-50% of normal
Weakness	47	14	11	22
Headache	46	14	11	21
Sweating	44	14	10	20
Nausea and vomiting	42	14	11	17
Salivation	31	13	8	10
Miosis	25	14	6	5
Dyspnea	23	14	6	3
Difficulty in walking	22	14	8	0
Diarrhea	21	9	4	8
Muscular fasciculation	20	14	6	0
Disturbance in speech	20	14	6	0
Disturbance in consciousness	19	14	5	0
Abdominal pain	15	5	4	6
Fever	15	9	6	0
Bronchopharyngeal secretion	14	10	4	0
Increased blood pressure	12	10	2	0
Loss of pupillary reflex	10	10	0	0
Cramp	9	9	0	0
Cyanosis	8	8	0	0

*As percent of value of each patient after recovery from poisoning.

Note: Modified from Nambe, T., C. T. Nolte, J. Jackrel, and D. Grob. 1971. Poisoning due to organophosphate insecticides: acute and chronic manifestations. Am. J. Med. 50:475-492. Reprinted with permission from author and publisher.

PERMISSIBLE EXPOSURE LIMITS

The Federal standards for parathion and malathion are 0.1 mg/m^3 and 15 mg/m^3, respectively. NIOSH has a recommended limit for parathion of 0.05 mg/m^3 (TWA) and a limit for methyl parathion of 0.2 mg/m^3 (TWA).

HARMFUL EFFECTS

Mild organophosphate poisoning causes symptoms of headache, fatigue, dizziness, blurred vision, excessive sweating, nausea and vomiting, stomach cramps, diarrhea, and salivation. These symptoms are similar to those of many diseases not related to pesticide exposure such as influenza, heat stroke, heat exhaustion, and gastroenteritis.

Moderately severe organophosphate poisoning causes all of the symptoms found in mild poisoning, but in addition, the patient is unable to walk, often complains of chest discomfort and tightness, exhibits marked miosis (constriction of the pupils), and exhibits muscle twitching. These symptoms might be reasonably mistaken for such conditions as pneumonia, myocardial infarction, and encephalitis.

Severe organophosphate poisoning may result in rapid onset of unconsciousness, local or generalized seizures, and other manifestations of a cholinergic crisis.

CLINICAL NOTES

An important clinical observation, in addition to those previously mentioned (high index of suspicion, history, clinical manifestations), which aids in the substantiation of the diagnosis of an anticholinesterase intoxication, is atropine refractoriness. When a larger than normal dose of atropine is given to a person not exposed to anticholinesterase pesticides, the early signs of atropine toxicity soon become apparent. These signs include dry mouth, flushed skin, increased heart rate, and dilated pupils. If the patient has anticholinesterase poisoning, large doses of atropine are required to produce these normal reactions.

The atropine test should be used with caution in patients with glaucoma. However, in acutely toxic patients suspected of organophosphate poisoning, immediate atropine therapy must be initiated even without tests of atropine refractoriness.

Acholest screening tests provide a simple but crude index of the degree of cholinesterase inhibition while offering the most immediate confirmation that is within the laboratory expertise of any hospital or clinic. Plasma cholinesterase determinations of this nature use filter paper impregnated with a pH-sensitive color reagent and can detect inhibition as low as 20 percent of serum cholinesterase. Plasma and red blood cell cholinesterase are more precise determinations, but errors have resulted from unfamiliarity of laboratory personnel with these procedures.

Treatment for parathion poisoning has been improved with the availability of 2-PAM (2-pyridine-aldoxime methiodide). Blood samples for cholinesterase determinations must be collected before 2-PAM treatment is started.

In severe cases it may be necessary to begin treatment with atropine

or 2-PAM before laboratory confirmation of significant cholinesterase depression is obtained.

TREATMENT

SPEED IS IMPERATIVE.

Principles of treatment include the immediate injection of atropine to block parasympathetic effects of the accumulated acetylocholine and of 2-PAM to reactivate the phosphorylated enzyme.

It is imperative to keep the airway open.

When the compound is ingested, it is important to act quickly to prevent any further systemic absorption.

When exposure is by skin contact, the compound should be rapidly removed by thorough rinsing or washing with water or soap and water. Compound splashed in the eye should be washed out with water, isotonic saline, or other ophthalmic irrigating solution, as available.

Wear rubber gloves while washing contact area to prevent any danger to medical personnel.

CARBAMATES

Carbamates are reversible cholinesterase inhibitors. Like organophosphates, they may be direct or delayed in action. Inhibition of the enzyme is reversed largely by hydrolysis of the carbamylated enzyme and to a lesser extent by synthesis of a new enzyme. Important carbamates are:

Baygon	Vapam
Carbaryl (Sevin)	Zectran
Thiram	

PERMISSIBLE EXPOSURE LIMITS

The Federal standard for carbaryl is 5 mg/m^3.

HARMFUL EFFECTS

Signs and symptoms of intoxication may include miosis, salivation, profuse sweating, lassitude, muscle incoordination, nausea, vomiting, diarrhea, epigastric pain, tightness in the chest, etc.

CLINICAL NOTES

2-PAM and other oximes are contraindicated for routine use.

Cholinesterase reactivates rapidly after carbamate poisoning. Laboratory cholinesterase determinations may be misleading.

LABORATORY NOTES

1-Naphthol, normally found in traces, is excreted in the urine in much higher concentrations following carbaryl ingestion.

TREATMENT

SPEED IS IMPERATIVE

Principles of treatment are similar to those used in organophosphate poisoning (atropine and maintenance of adequate respiration) with the exception of the use of 2-PAM.

CHLORINATED HYDROCARBONS

Chlorinated hydrocarbon insecticides are more persistent in the environment than most other synthetic organic pesticides, and because of this, their use has recently decreased. Among the most important chlorinated hydrocarbons are the following:

Benzene Hexachloride (BHC)	Kepone
Chlordane	Heptachlor
DDT	Lindane (Isomer of BHC)
Dicofol (Kelthane)	Mirex
Dieldrin	Thiodan
Endrin	Toxaphene

HARMFUL EFFECTS

Chlorinated hydrocarbons are most efficiently absorbed by ingestion. In general, they act on the central nervous system to stimulate or depress. Signs and symptoms of toxicity, therefore, vary with the specific chemical. Symptoms have been reported as soon as 30 minutes after massive exposure, but generally develop more slowly; if this pattern of symptoms does not appear within a few hours after suspected acute exposure, another diagnosis or complicating feature must be sought.

Mild chlorinated hydrocarbon poisoning causes such symptoms as dizziness, nausea, abdominal pain, and vomiting. In chronic poisoning, loss of weight and appetite, and, in the case of endrin, temporary deafness and disorientation may occur.

Moderately severe chlorinated hydrocarbon poisoning presents mild signs followed by severe irritability, convulsive seizures, and coma. Seizures may be epileptiform in character with frothing at the mouth, facial congestion, violent convulsive movements or stiffness of the limbs, associated with stupor or coma. In severe cases, the convulsions may be continuous, with elevated body temperatures, unconsciousness, labored breathing with vigorous, rapid heart beat, and eventually death.

CLINICAL NOTES

Vomiting should NOT be induced when the ingested pesticide is in a hydrocarbon solvent. Epinephrine should not be given since chlorinated hydrocarbons may sensitize the heart to catecholamines.

LABORATORY NOTES

A high urinary level of organic chlorine or especially of p-chlorophenyl acetic acid indicates exposure to DDT or to one of the analogous compounds. The level, however, is not necessarily indicative of the severity of exposure.

TREATMENT

In cases of ingestion, gastric lavage should be performed.

Care should be taken to prevent aspiration of gastric contents. In some cases, induction of catharasis with aqueous solutions of sodium

sulfate has been of value in increasing fecal excretion and retarding absorption. Barbiturates are sometimes helpful in reducing convulsions. Respiration should be closely followed. Oil, oily cathartics (e.g., mineral oil), and epinephrine should be avoided.

BIPYRIDYLS

Bipyridyls include paraquat and diquat and are used in the form of the dichloride, dibromide, or dimethosulfate salt.

HARMFUL EFFECTS

Most reported cases involved accidental ingestion which produced proliferative changes in the lungs, cornea, lens, nasal mucosa, skin, and finger nails.

With the exception of eye lesion, illness due to occupational exposure is usually mild and is the result of skin contact.

CLINICAL NOTES

Diquat affects the lens and the gastrointestinal mucosa. It does not produce the lung changes characteristic of paraquat.

The clinical picture following accidental or suicidal ingestion of paraquat is very different. Paraquat ingestions are frequently fatal. Their management is unsatisfactory and largely symptomatic. Three clinical stages follow ingestion of as little as one ounce of paraquat.

The first is a gastrointestinal phase with burning in the mouth and throat, nausea, vomiting, abdominal pain, and diarrhea.

Several days after exposure, signs of hepatic and renal toxicity appear. These are due to central zone necrosis of the liver and acute tubular necrosis of the kidney.

Ten to 20 days after ingestion, progressive proliferative changes develop in the lungs. Hyperplastic changes in the terminal bronchioles occur with alveolar fibroblastic proliferation. Loss of lung surfactant has been demonstrated. Within a few days, death from respiratory failure occurs.

LABORATORY NOTES

Urinary studies have indicated that 90 percent of the ingested paraquat is excreted in the first 24 hours. Delayed pulmonary effects appear to be the result of an irreversible process that develops long after the initial stimulus has gone.

Paraquat is poorly absorbed from the gastrointestinal tract. Excretion data suggest that only 1 to 5 percent of the ingested material is absorbed in man. Maximal blood concentrations are reached within 4 to 6 hours after ingestion.

TREATMENT

Treatment is primarily directed toward decreasing the amount of paraquat absorbed and the concentration in the circulating blood. This may be achieved by appropriate repeated administration of large amounts of adsorbents and purgatives.

RODENTICIDES

Rodenticides of first importance include sodium fluoroacetate, strychnine, thallium sulfate, and warfarin. For information on rodenticides containing arsenic, barium, cyanide, and phosphorus, reference may be made to the appropriate chemical in the section on Chemical Hazards.

SPECIAL NOTES

Fluoroacetate is a highly toxic poison which causes central nervous system stimulation (convulsions) and cardiac arrhythmias. Specific treatment includes monacetin (monoacetin, glycerol monoacetate).

Strychnine poisoning is characterized by severe convulsion without loss of consciousness. Death is usually a result of asphyxia or involvement of vital brain centers. The compound may be identified in the urine soon after ingestion.

Thallium sulfate by ingestion or skin absorption may induce intoxication. Acute poisoning is characterized by severe gastroenteritis following a latent period of 12 to 24 hours. Other effects may include liver and kidney damage, encephalopathy, neuritis, ataxia, and alopecia. Recovery is slow. Thallium may be demonstrated in the urine.

Warfarin — See Coumarins.

Coumarins and *Indandiones* include Diphacin, Fumarin, Pival, (Pivalyn), PMP, Valone, and warfarin.

After repeated ingestion for several days, symptoms may include bleeding from the nose and gums, and into the conjunctiva, urine, and stool. Other possible symptoms are pallor, petechial rash, massive ecchymoses, hematoma of skin and joints, brain hemorrhage, etc. Shock and death may follow.

Laboratory determination of prothrombin time may be helpful in assessing the extent of exposure.

FUNGICIDES

The fungicides are a heterogeneous group of chemicals and, with the major exception of the dithiocarbamates, have been in use for many years. Many of the fungicides such as formaldehyde, furfural, phenol, tetramethylthiuram disulfide and compounds of boron, chromium, copper,

mercury, tin, and zinc (some of which are also used as herbicides and insecticides) are discussed in the section on Chemical Hazards.

The dithiocarbamates include ferbam (ferric dimethyldithiocarbamates), ziram (zinc dimethyldithiocarbamate), maneb (manganous ethylene bisdithiocarbamate), nabam (disodium ethylene bisdithiocarbamate), and zineb (zinc ethylene bis-dithiocarbamate). Their chief adverse effects are irritation of the skin, eyes, and upper respiratory tract.

HERBICIDES

Herbicides, or weed killers, may be classified as pesticide chemicals. They can kill plants on contact, or they can be translocated, that is, absorbed by one part of the plant and carried to other parts where they exert their primary toxic effect. Most of the commonly used herbicides (ammonium sulfamate, dalapon, phenoxyacetic acid derivatives (e.g., 2,4,5—T), carbamate derivatives, petroleum oils, sodium borate, Crag herbicide) have a low toxicity and have caused little difficulty among users.

Some herbicides pose more serious problems; for example, the methemoglobinemia and central nervous system depression produced by sodium chlorate. Pentachlorophenol, a metabolic stimulant, has been responsible for several deaths because of hyperthermia. Pentachlorophenol through skin absorption can also result in peripheral motor neuropathies. Amino triazole has produced cancer in experimental animals, but there have been no untoward effects reported in man.

Herbicides with cutaneous effects include trichloroacetic acid, a corrosive irritant of the skin and mucous membranes; pentachlorophenol, a producer of a primary irritant type of contact dermatitis; and creosote, a primary irritant and photosensitizer.

Reference may be made to chemicals in the section on Chemical Hazards for the toxicity of the following herbicides: arsenic trioxide and sodium arsenate (see Arsenic), copper sulfate (see Copper and Compounds), creosote compounds, (see Cresol and Phenol), dinitrophenols (see Dinitrophenol), kerosene, and phenylmercuric acetate (see Mercury and Compounds).

FUMIGANTS

Fumigants are pesticides which may be applied in the solid, liquid, or gaseous state. A combination of high volatility with high pest toxicity is generally desired; however, compounds with low volatility may be preferred for soil fumigation. The possibility of excessive exposures exists wherever fumigants are used, as in fumigating grains, soils, clothes, furs, homes, warehouses, barns, ships, mills, freight cars, and greenhouses.

Each of the following compounds has found use as a fumigant.

Because they have other industrial applications as well, they are discussed individually in the section on Chemical Hazards.

Acrylonitrile
Carbon Disulfide
Carbon Tetrachloride
p-Dichlorobenzene (see Chlorinated Benzenes)
Dioxane
Ethylene Dibromide
Ethylene Dichloride
Ethylene Oxide
Hydrogen Cyanide
Methyl Bromide (see Bromine and Compounds)
Methylene Chloride
Methyl Formate
Naphthalene
Perchloroethylene
Propylene Dichloride
Sulfur Dioxide
Tetrachloroethane
Trichloroethylene

MISCELLANEOUS INSECTICIDES

Although the newer synthetic pesticides previously discussed in this section are becoming increasingly popular, the following compounds continue to find significant usage.

Lead Arsenate and Arsenite

These compounds enter the body by inhalation, ingestion, or percutaneous absorption. Signs and symptoms of poisoning are similar to those characteristic of lead or arsenic intoxication. Acute symptoms include nausea, vomiting, abdominal pain, diarrhea, muscle cramps, excitation, and disorientation. Chronic poisoning is manifested by anorexia, weakness, weight loss, pallor, colic, diarrhea, peripheral neuritis, hepatitis, and nephritis. A vesicular dermatitis has frequently been reported. The carcinogenic hazard from chronic arsenic exposure also cannot be ignored.

Nicotine

Nicotine is an extremely toxic alkaloid capable of producing nervous system stimulation followed by severe nervous system depression. The effects may result from ingestion, inhalation, or rapid percutaneous absorption of the material. Analysis for urinary nicotine may aid in the diagnosis.

Pyrethrum

Pyrethrum does not appear to be particularly toxic; however, pri-

mary contact dermatitis and allergic skin and pulmonary reactions have occurred following minimal exposure to the dust.

Rotenone

Rotenone is a plant extract which is more toxic than pyrethrum but, as normally used, is not excessively hazardous. Contact dermatitis and numbness of the oral mucous membranes may follow sufficient exposure.

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