Chapter 9

LONG-TERM HEALTH EFFECTS OF CHEMICAL THREAT AGENTS

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INTRODUCTION

Chemical warfare agents were used extensively in World War I (the United States had approximately 70,000 chemical casualties[1]) and have been employed or allegedly employed in about a dozen conflicts since then.[2] The most recent large-scale use of these weapons was by Iraq in its war with Iran in the late 1980s. During that conflict, Iraq used nerve agents and the vesicant mustard[3]; after the war it maintained stockpiles of the two agents and the capability to manufacture them. Before coalition forces liberated Kuwait early in 1991 during the Persian Gulf War, Iraq was expected to use these agents when attacked. No reports of the use of chemical weapons during that conflict were made, however, despite the vigilance of the press corps and military medical personnel, who were trained to report, investigate, and care for chemical casualties.[4,5] One US soldier developed skin blisters 8 hours after exploring an underground bunker.[4] His clinical findings and mass spectroscopy readings (performed by a chemical detection team) from his clothing and the bunker supported a diagnosis of accidental mustard exposure, which was mild. The exposure was not confirmed by later testing of clothing samples, from which trace amounts of the agent may have dissipated.

Although the acute effects of the nerve agents and of mustard agent are well known,[6,7] the long-term effects after a single exposure or multiple exposures are less well recognized. The nerve agents are the subject of Chapter 5, Nerve Agents, and mustard is discussed in Chapter 8, Vesicants. This chapter focuses on the long-term effects of exposure to these agents.

MUSTARD

Two well-known forms of mustard exist. Sulfur mustard (designated by the military as H or HD) was first synthesized in the early 1800s, has been used in warfare on several occasions, and is a major chemical warfare agent.[6] Nitrogen mustard is of more recent origin, has not been used in warfare, and is a cancer chemotherapeutic agent. In this chapter, the word "mustard" will refer to sulfur mustard.

Mustard is best known as a skin vesicant, but in a series of Iranian patients exposed to mustard, 95% had airway effects, 92% had eye injuries, and 83% had skin lesions.[8] After absorption, mustard, an extremely potent alkylating agent, has the potential to damage all cells and all organs.[6] Absorption and systemic distribution of a significant amount of mustard damages the bone marrow, where it destroys the precursor cells, resulting in pancytopenia.[6] Less commonly, clinical effects are seen in the gastrointestinal tract (usually as a terminal event)[9,10] and in the central nervous system (CNS), with ill-defined symptoms such as lethargy and apathy.[8,11]

On the skin, a Ct (the concentration [C] of agent vapor or aerosol in air, as mg/m^3, multiplied by the time [t] of exposure, in minutes) of 50 mg•min/m^3 or a droplet of 10 μg of mustard is adequate to produce vesication.[6] (One study[12] indicates that 8 of the 10 μg evaporate and 1 μg enters the systemic circulation, leaving 1 μg to produce the skin lesion.) Eye lesions can be produced by a Ct of 10 mg•min/m^3.[13] Airway injury occurs at a Ct of 100 mg•min/m^3 or higher.[6]

The mode of biological activity of mustard is less well defined than that of the nerve agents. The initial event is felt to be a reaction of mustard and deoxyribonucleic acid (DNA) with subsequent damage to the DNA. A series of intracellular events then occur, leading to cellular damage accompanied by inflammation and cellular death. Cellular damage begins within 1 to 2 minutes of contact of mustard to skin or mucous membranes.[6] The onset of clinical effects following exposure to mustard occurs hours after the exposure.[6] The delay usually ranges from 2 to 24 hours, is inversely proportional to the amount of mustard, and depends on other factors as well. No specific therapy for mustard exposure exists.[6] Decontamination within a minute or two will prevent or diminish the lesion, and later care consists of symptomatic management of the lesion.

Studies have established that the chemical agent mustard has long-term sequelae. Both Morgenstern et al[14] and Buscher[15] emphasize that chronic low-dose exposure over months to years in occupationally exposed workers leads to chronic bronchitis, bronchial asthma, hoarseness, aphonia, and hypersensitivity to smoke, dust, and fumes. Affected individuals typically show persistent disability, with increased susceptibility to respiratory tract infections and evidence of bronchitis and bronchiectasis.[6,14,15] Laboratory animal studies[16–18] have found that mustard is mutagenic and carcinogenic, and it is reported to be carcinogenic in humans.[19]

A 1993 study[19] sponsored by the Veterans Administration and conducted by the Institute of Medicine reported that a causal relationship exists between mustard exposure and the following conditions:

- chronic respiratory diseases (asthma, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, chronic laryngitis);
- respiratory cancers (nasopharyngeal, laryngeal, and lung);
- pigmentation abnormalities of the skin;
- chronic skin ulceration and scar formation;
- skin cancer;
- chronic conjunctivitis;
- recurrent corneal ulcerative disease;
- delayed recurrent keratitis;
- leukemia (nitrogen mustard);
- bone marrow depression and (resulting) immunosuppression;
- psychological disorders (mood disorders, anxiety disorders, and traumatic stress disorders); and
- sexual dysfunction as a result of scrotal and penile scarring.

Although laboratory evidence suggests that all of these *might* occur, there is no data in humans to indicate that all *have* occurred. The study report recognized this by stating, "It is also possible that skin cancers did not occur in the studied populations…"[19] and "…underrepresented in human studies is information on chronic or delayed effects [on the bone marrow and immune system]."[19] The report also pointed out that the psychological disorders were from the stress of the exposure and not from the agent, and there seemed to be no data on sexual dysfunction. Moreover, it is not clear from the report whether these effects follow one or multiple mustard exposures.

All human studies dealing with chronic mustard disease processes are retrospective and fraught with the problems inherent in retrospective studies. These problems include bias in the sampling populations; lack of epidemiological controls for the effects of smoking, lifestyle, race, gender, age, or exposure to other chemicals; differential quality of available health care; and incorrect diagnosis.[6] These limitations make absolute interpretation of the studies difficult.

Over the past several years, Iranian investigators have provided a number of papers that study the late toxic effects of mustard exposure in patients 16 to 20 years after the Iran-Iraq conflicts of the 1980s.[20–26] Balali-Mood and Hefazi[27] have summarized most of these data in a comparative review of early and late toxic effects of mustard.

Carcinogenesis

Mustard is an alkylating agent similar to drugs that have been used in cancer chemotherapy, such as nitrogen mustard, Cytoxan (Bristol-Myers Squibb Oncology Division, Princeton, NJ), and methotrexate. Since DNA is one of mustard's most sensitive targets, it is not surprising that carcinogenesis and radiomimetic effects are seen.

In studies[18,28,29] conducted from 1949 through 1953 by WE Heston with mustard and strain-A mice (immunocompromised), the occurrence of pulmonary tumors was easily demonstrated. Studies conducted at Edgewood Arsenal, Maryland, examined the carcinogenic effects on rats in whole-body chamber exposures. Mustard readily produced skin malignancies in rats, but no excess tumors at other sites.[30] Subcutaneous injections totaling about 6 mg/kg of mustard produced sarcomas and other malignancies at injection sites in C3H, C3Hf, and strain-A mice, but did not result in an increase of malignancies at other sites.[29]

Human data on the carcinogenicity of mustard are from *(a)* battlefield exposures, *(b)* accidents, and *(c)* workers in chemical factories. Both British and American studies have investigated the increased incidence of pulmonary carcinoma arising from World War I battlefield exposure. All are difficult to interpret, owing to the lack of controls for age, chronic pulmonary disease, cigarette smoking, and other factors that might have affected the outcome.[31–33]

In contrast to battlefield exposures, studies of factory workers involved in the production of mustard have shown a definite link between prolonged exposure to low doses of mustard and cancer.[6] Several studies[17,34–38] have provided evidence of an increased risk of respiratory tract cancers in factory workers. Easton et al[35] found a 45% increase in deaths due to lung cancer, a 170% increase in death from cancer of the larynx, and a 450% increase in deaths from cancer of the pharynx, compared with expected deaths in the general population. The risks for cancer of the pharynx and lung were significantly related to the duration of employment at the factory. For reasons analyzed more fully elsewhere,[39] the association between a single exposure to mustard and airway cancer is not as well established.

Japanese studies suggest a greater potential risk of cancer from mustard than do the British studies. Easton et al[35] and Manning et al[17] suggest that the difference is related to the design of the Japanese studies and to the lower industrial hygiene standards in Japan at the time of the studies.[6] The weight of the evidence—cellular, epidemiological, and toxicological—indicates a causal association between mustard exposure and the occurrence of excess respiratory cancer, skin cancer, and possibly leukemia. Inadequate exposure information limits accurate estimation of the cancer excesses that may be expected.[19]

The Iranian data suggest that surviving victims of mustard exposure during the Iran-Iraq War are exhibiting carcinoma of the nasopharynx, bronchogenic carcinoma, and adenocarcinoma of the stomach, as well as acute myeloblastic and lymphoblastic leukemia.[27] Definitive studies of the nature and types of cancers seen in this patient population have yet to be published.

Chronic Pulmonary Disease

Inhalation of mustard vapor primarily affects the laryngeal and tracheobronchial mucosa.[6] Evidence suggests that mustard inhalation causes sustained respiratory difficulties even after the acute lesions have healed. Clinical follow-ups on 200 Iranian soldiers who were severely injured by mustard during the Iran–Iraq War indicate that about one third had experienced persistent respiratory effects 2 years after initial exposure. Reported problems included chronic bronchitis, asthma, rhinopharyngitis, tracheobronchitis, laryngitis, recurrent pneumonia, bronchiectasis, and in some cases, severe, unrelenting tracheobronchial stenosis.[22,40–43]

Of the British soldiers exposed to mustard in World War I, 12% were awarded disability compensation for respiratory disorders that were believed to be from mustard exposures during combat.[44] Bronchitis was the major complaint; emphysema and asthma were also reported. However, epidemiological studies of the relationship between agent exposure and subsequent respiratory disability were severely limited for several reasons. Often, individuals had experienced multiple combined exposures to mustard and other chemical agents. Also, influenza and other respiratory ailments frequently made diagnosis of the mustard vapor injury difficult.[6] Finally, no epidemiological controls for smoking or for postexposure environmental and occupational histories were included in the studies.[45]

Wada et al[34] suggest a causal relationship between mustard exposure and subsequent bronchitis, tuberculosis, and pneumonia in factory workers involved in the production of mustard. Again, Morgenstern et al[14] and Buscher[15] emphasize that chronic low-dose exposure over prolonged periods (presumably months to years) leads to lingering bronchitis, bronchial asthma, hoarseness, aphonia, and hypersensitivity to smoke, dust, and fumes. Affected individuals typically show persistent disability, with increased susceptibility to respiratory tract infections and evidence of bronchitis and bronchiectasis.[6]

Little contemporary information regarding the pathogenesis of the respiratory lesions is available, and few data from people or animals exposed to nonlethal concentrations of mustard vapor exist. Even fewer studies investigate the histopathology of the recovery process in animals exposed to mustard.[19] However, two studies[9,46] conducted during World War I suggest that low-level exposure or survivable exposures in dogs and rabbits may produce scar tissue following small ulcerations in the trachea and larynx, causing contractions of these areas. The more severe respiratory tract lesions described in animals exposed to mustard vapor appear to be similar in type and location to those described in humans.[6]

The Iranian database shows that in the 3-year postexposure time frame the most severely affected patients demonstrated restrictive pulmonary disease patterns. By 16 years postexposure, these patterns had become obstructive in nature.[27] Sixteen to twenty years after exposure, the main respiratory complications were chronic obstructive pulmonary disease, bronchiectasis, asthma, large airway narrowing, and pulmonary fibrosis.[27]

Chronic Eye Disease

Individuals who sustain acute ocular injury from high-dose mustard exposure may experience difficulties even after the initial effects of the injury have subsided.[47–50] Recurrent or persistent corneal ulceration can occur after latent periods of 10 to 25 years. This delayed keratopathy[49,51] may be accompanied by chronic conjunctivitis and corneal clouding. Anecdotal accounts suggest that low-dose exposure also causes increased sensitivity to later exposures to mustard,[52] although the existence of increased sensitivity is difficult to substantiate with available scientific evidence.[6] About 10% of those with eye injury in World War I had severely affected eyes, with both the cornea and the conjunctiva being involved. Members of this group developed the "delayed keratitis" noted above 8 to 25 years later.[48]

The 1993 Institute of Medicine study[19] of the effects of mustard and lewisite exposure on the health of veterans concluded that acute, severe injury of the eye from mustard might result in recurrent corneal ulcerative disease for the remainder of the patient's life, with a maximum incidence occurring 15 to 20 years after the injury. Based on extensive data, the study concluded that a causal relationship between severe exposure to mustard and the development of delayed recurrent keratitis exists.[47] The study also found a causal relationship between exposure to mustard and the development of prolonged, intractable conjunctivitis.

Scarring of Epithelial Surfaces

Residual cutaneous lesions most often take the form of scars that result from uncontrolled fibroblastic activity and overgrowth of connective tissue during the process of wound repair. Even wounds that are well cared for on joints and sites that are not easily immobilized, such as shoulders, knees, elbows, and male genitalia, often heal with severe residual scar formation. Pigmentation is often altered (either increased or decreased) at these sites, although the degree of alteration does not differ from that observed in injuries caused by burns and other forms of physical and chemical insult. In the absence of melanocyte destruction, hyperpigmentation predominates. If melanocytes are locally destroyed, and inward migration from destroyed adnexal structures does not occur, depigmentation predominates. In a prospective study of delayed toxic effects from mustard exposure, Balali-Mood[22] followed a group of Iranian solders exposed to mustard gas during the Iran–Iraq War. After 2 years, 41% of the exposed victims were experiencing pigmentary disorders. Any previously injured sites have been described as being "sensitive" to subsequent mechanical injury. These sites may show recurrent blisters after mild injury.[19] Renshaw[12] reported on the development of contact sensitivity in humans following localized exposure to liquid mustard. Cutaneous sensitivity may be seen within 8 days following the first application, and a more pronounced effect is seen after 4 weeks. The incidence of hypersensitivity varies between 30% and 65% of exposed individuals. Sensitivity may be immediate hives or delayed dermatitis and appears to last a lifetime. Sensitivity may also take the form of flares of old, healed mustard injury sites after a fresh application of mustard to normal, unaffected skin.[12] The occurrence of skin cancers at the site of old scar formation is an acknowledged biological phenomenon.[53,54] Cutaneous cancers resulting from acute mustard exposure usually localize in scars, whereas those caused by chronic exposure can occur on any exposed site.[55]

In its study of mustard and lewisite effects,[19] the Institute of Medicine concluded that the evidence indicates a causal relation between acute, severe exposure to mustard agents and increased pigmentation and depigmentation in human skin; acute and severe exposure can lead to chronic skin ulceration, scar formation, and the development of cutaneous cancer (but see the caveat in the previous discussion of this report's conclusions); and chronic exposure to minimally toxic and even subtoxic doses can lead to skin pigmentation abnormalities and cutaneous cancer. Among the Iranian victims at 16 to 20 years after exposure, the most common skin lesions, by order of occurrence, were hyperpigmentation, erythematous popular rash, dry skin, multiple cherry angioma, atrophy, and hyperpigmentation.[27]

Central Nervous System

Excitation of the CNS after mustard exposure, resulting in convulsions and followed by CNS depression, has been reported.[56] Convulsions and cardiac irregularities appear to occur only after extremely acute, high doses,[57] which are probably attainable only in laboratory settings.[6] Mustard casualties of the Iran–Iraq War did not display severe CNS or cardiac abnormalities.[40]

Acute neuropsychiatric symptoms, including severe depression and changes in mentation, are common after high-dose exposures to mustard agents. These symptoms are produced both directly by the chemical and secondarily to other physiological changes.[19] Follow-up of workers in German chemical warfare plants showed a high prevalence of various neurological disorders, including impaired concentration, diminished libido, and sensory hypersensitivity.[58] To what extent mustard agents were responsible is not clear because multiple exposures to other agents, including nerve agents, were known to have occurred.

Balali-Mood et al[23] conducted studies on peripheral neuropathic processes in victims exhibiting severe late manifestations of mustard poisoning using electromyography and nerve conduction velocity. Seventy percent of the patients demonstrated disturbances in the peripheral nervous system. Nerve conduction abnormalities were more common in sensory nerves and more prevalent in lower extremities than in upper extremities. Forty percent of the patients exhibited incomplete interference patterns in electromyographic studies.

Mutagenesis, Teratogenesis, and Reproductive Toxicity

Mustard causes cross-linking of DNA and is known to alkylate DNA at the O^6 position of guanine. Some authors[59,60] suggest that intrastrand DNA cross-links, rather than interstrand cross-links,[61,62] are the lesions primarily responsible for producing chromosomal aberrations. Mustard causes chromosomal breakage and induces sister chromatid exchanges in a wide variety of cells including mammalian cells.[63] The International Agency for Research on Cancer in Lyon, France (an agency of the World Health Organization),

has classified mustard as a human carcinogen based on the findings of epidemiological studies. Taken together, these observations highlight the potential of this compound to induce genetic damage and become a long-term health hazard. The agency also suggests that mustard could be a reproductive toxin.[19]

The 1993 Institute of Medicine report[19] noted that the quality of human data on the reproductive toxicity of mustard is quite poor. Follow-up of the occupational or battlefield cohorts to determine the nature of any reproductive toxicity or teratogenic effects attributable to these exposures has been insufficient. The evidence suggests a causal relationship between mustard exposure and reproductive toxicity in laboratory animals, but the database is far too small and unreliable to allow a clear understanding of human reproductive risk from exposure to mustard. Mustard can cause genetic alterations in the sperm of male rats after inhalation or gastric exposure, but rodent studies[64] showed that mustards are not detectable teratogens in animals. The human data are insufficient for reliable interpretation.[19]

NERVE AGENTS

Nerve agents are esters of phosphonic acid and are extremely potent chemicals. Their military designations are GA (tabun), GB (sarin), GD (soman), GF (cyclosarin), and VX. The agent VX has no common name. In contrast to the information available on both short- and long-term effects of mustard in humans from its battlefield use in World War I and the Iran–Iraq War, and from experimental studies during the World War I and World War II periods,[19] limited data from the battlefield use of nerve agents are available.

The toxic effects of nerve agents are caused primarily by their inhibition of acetylcholinesterase (AChE) and the resulting accumulation of acetylcholine.[65] Other biological activities of these agents have been described, but the relation of these activities to clinical effects has not been recognized. For example, some nerve agents affect ionic channels,[66] and all affect structures other than AChE.[67] Several milligrams of VX, the least volatile nerve agent, absorbed through the skin causes clinical signs and symptoms.[68,69] A Ct of 2 to 3 mg•min/m^3 of sarin produces miosis and rhinorrhea in humans.[70] This Ct can be attained with exposure to a concentration of 2 mg/m^3 for 1 minute or a concentration of 0.05 mg/m^3 for 40 minutes. The initial signs of exposure to small quantities of agent vapor are miosis, rhinorrhea, and airway constriction.[7,71] Larger amounts cause loss of consciousness, seizure activity,[71] cessation of respiration[72] and cardiac activity, and death, unless there is medical intervention. Effects occur within minutes of exposure,[71,72] and after a large exposure (Ct of 10–200 mg•min/m^3, depending on the agent[73]), death occurs in 10 to 15 minutes. After exposure to a sublethal amount on the skin (1–3 mg), the onset time for clinical effects may be hours.[68,69] The initial effect is usually vomiting, which may be followed by muscular weakness. A lethal amount of VX on the skin causes effects within several minutes,[71] and death occurs shortly afterwards.

Treatment consists of the administration of atropine, a drug that blocks the effects of the excess acetylcholine at muscarinic cholinergic receptor sites, and of 2-pyridine aldoxime methyl chloride (2-PAM Cl, also called 2-pralidoxime chloride), an oxime that removes the agent from AChE, thereby reactivating the enzyme after poisoning by some agents.[74] 2-PAM Cl, however, is ineffective against soman intoxication[71] because of soman's rapid aging. (Aging is the process by which one of the nerve agent's alkyl groups leaves the molecule after binding to AChE. After dealkylation, an AChE-bound nerve agent molecule can no longer be removed from the enzyme by an oxime. The aging half-time of soman is about 2 min.) Ventilatory support is necessary when breathing has stopped or is inadequate,[71,72] and the anticonvulsant diazepam may need to be administered.

Information on the effects of nerve agents in humans comes from the accidental exposure of hundreds of people mildly or moderately exposed while working with nerve agents and from a handful of workers who had severe exposures. Investigational studies carried out in hundreds of people also provide information. More recently, terrorists used sarin in two separate attacks in Matsumoto and Tokyo, Japan, in 1994 and 1995. These attacks have provided a great deal of information on both the short- and long-term impact of organophosphorus nerve agents in humans. Information on the effects of organophosphorus insecticides is also included so that medical officers can compare and contrast the two. Because both nerve agents and insecticides are organophosphorus compounds, people often tend to extrapolate the biological effects of one to the other, but in fact there are many differences between the two. The authors of some reports did not recognize the differences and grouped them together.[75,76]

Although the organophosphate insecticides are similar to nerve agents in inhibiting cholinesterase, they differ in other characteristics. For example, the cholinergic crisis caused by acute, severe intoxication with the insecticides is generally much longer than that caused by nerve agents (days to weeks for

insecticides[77–79] vs hours for nerve agents[71,72]). Not only do insecticides differ from nerve agents, but they also differ among themselves in some of their biological effects; for example, some cause polyneuropathy, and others do not.[79] Because of these differences, all of which have probably not been defined, the similarity between the effects of insecticides in humans and the effects of nerve agents in humans cannot be assumed. (As stated earlier, insecticides are included here only so that the similarities and differences can be noted; readers should be careful not to confuse the two.)

Polyneuropathy

Insecticides

Organophosphorus ester–induced delayed neurotoxicity (OPIDN) has been recognized as a clinical syndrome in humans and animals for over 50 years. After exposure to certain organophosphates, incoordination, ataxia, spasticity, and flaccid paralysis develop over the following 1 to 3 weeks; the paralysis begins distally in the lower limbs and eventually spreads to the upper limbs. Part or all of the lesion may be reversible, but in its most severe form it can cause lifetime quadriplegia. Structural changes begin at the distal, nonmyelinated portion of the nerve, followed by progressive demyelination associated with degeneration of more proximal nerve segments.[79] This syndrome was initially associated with ingestion of triorthocresyl phosphate rather than an insecticide. After organophosphate insecticides became available, the syndrome was seen after exposure to some, but not all, of them.[79]

The best animal model for studying the effects of exposure to organophosphates is the chicken.[80,81] Extensive studies have been performed to elucidate the mechanism of action that causes OPIDN and to screen new organophosphate insecticides for this effect.[79,80] The exact mechanism of action is still unknown, but much evidence suggests that the inhibition of neurotoxic esterase in nerve tissue is involved.[81] Administration of oximes and atropine has no effect on the production of this neurotoxicity.[82]

OPIDN is not seen with all insecticides.[79,80] Generally, insecticides that have been shown to cause polyneuropathy have been removed from the market; only those that have been demonstrated not to cause this effect in animal models are available.

Nerve Agents

Nerve agents have caused polyneuropathy in animals only at doses many fold greater than the LD^{50} (the dose [D] that is lethal [L] to 50% of the exposed population)—doses that require massive pretreatment and therapy to ensure survival of the animals. Davies et al[83] produced polyneuropathy in chickens with sarin only at 60 or more times the LD^{50}. (The animals were protected with atropine and oxime to permit survival.) Neuropathy was not detected at 8 times the LD^{50} of soman. Davies's group also detected no polyneuropathy at doses of VX of 45 μmol/kg.[84]

In another study,[85] polyneuropathy was found in hens after 30 to 60 times the LD^{50} for sarin was administered, but not at 38 times the LD^{50} for soman or 82 times the LD^{50} for tabun. VX was not examined in this study because its ability to inhibit neurotoxic esterase is negligible. At 120 times the acute LD^{50} in hens, soman and tabun caused polyneuropathy in some surviving animals.[86] Cyclosarin is a stronger inhibitor of neurotoxic esterase in vitro than the other nerve agents.[87] However, cyclosarin, in addition to tabun, soman, and VX, did not cause polyneuropathy at very high doses.[88]

Polyneuropathy has not been noted in the handful of humans severely exposed to nerve agents or in the hundreds of humans with mild-to-moderate effects from nerve agents. However, one report details a case study in which a patient who survived for 15 months following the Tokyo sarin terrorist attack showed distal sensory axonopathy on postmortem analysis.[89] The patient survived the initial attack, but was maintained on mechanical ventilation and total parenteral nutrition until he died of pneumonia. He initially showed signs of tremor and decerebrate rigidity, which changed to flaccid quadriparesis 6 months following the sarin intoxication. He then developed distal-dominant, severe muscle atrophy with clawhand and foot drop deformity. The postmortem analysis confirmed the distal axonopathy as well as severe hypoxic-ischemic CNS damage. Obvious limitations of this report include the fact that the patient was maintained for an extended period with life support and was largely immobile, and there is no information regarding the total sarin exposure the man received. Nevertheless, the case report is one of the first to show temporally delayed distal neuropathy in humans. Studies using smaller doses of tabun, sarin, and soman are described in the toxicology section later in this chapter.

Muscle Necrosis

Insecticides

Necrosis of rat skeletal muscle in the region of the motor endplate has been noted after administration of cholinesterase-inhibiting compounds in amounts sufficient to cause signs.[90] Swelling, eosinophilia, and

loss of striations of myofibers can be observed by light microscopy in the motor endplate regions as early as 2 hours after administration of the organophosphate, and the lesion is fully developed in 12 to 24 hours. In affected fibers, the sarcolemma remains intact and is the focus of later repair of the fiber. Recovery begins in 2 days and is complete by 2 weeks. The lesion can be prevented or lessened by denervation or by administration of atropine and oxime within the first 2 hours; the lesion is more severe in muscles of high activity, such as the diaphragm, and in type II fast-twitch muscle fibers.[90]

Muscle necrosis was seen in the diaphragm of a man who died after drinking parathion. No cholinesterase could be demonstrated in the myoneural junctions of any muscle, but necrosis was limited to the diaphragm. Each focus involved one to four sarcomeres of both types of myofibers, varying from acute swelling to vacuolar disintegration of the fibers. The nerve endings in the segmental necrotic zones were degenerated.[91]

Nerve Agents

The circumscribed muscular necrosis seen with insecticides has also been seen after sarin[92,93] and tabun[94] administration to experimental animals. Soman produced necrosis in one study,[95] but not in another.[94] On stimulation of the nerve, the muscle was unable to sustain a tetanic contraction at frequencies of 100 and 200 Hz.[93]

Intermediate Syndrome

Insecticides

A second type of delayed neurological manifestation of organophosphate insecticide poisoning is the "intermediate syndrome." In a series of 200 consecutive cases of organophosphate insecticide poisoning, 36 patients developed a weakness of the proximal muscles of the limbs, cranial nerve weaknesses, bilateral pyramidal tract signs, and areflexia.[96] This disturbance began 12 to 84 hours after hospital admission. In most cases, the cholinergic crisis had resolved, and the 21 patients who survived recovered completely by 96 hours. The lesion was unresponsive to large amounts of atropine; 2-PAM Cl was not available. The authors of the report[96] divided the signs of organophosphate intoxication into two groups, which they called type I and type II. According to these authors, type I signs were muscarinic in nature and were amenable to atropine therapy, whereas type II signs were nicotinic in nature, appeared 12 to 48 hours after exposure, and were resistant to atropine therapy.

Ten additional cases were later described.[97] These patients received atropine (up to 40 mg every 24 h) and 2-PAM Cl (1 g every 12 hour for 24 to 48 h) during the cholinergic-crisis phase. About 24 to 96 hours after poisoning, the 10 patients developed a syndrome that included palsies of cranial nerves III, IV, VI, VII, and X; weakness of the respiratory muscles (four patients required immediate intubation and assisted ventilation at the onset of the syndrome); weakness of the proximal limb muscles; and pyramidal tract signs. Recovery occurred in 5 to 18 days. Electromyography in limb muscles and nerve conduction were normal. Tetanic stimulation of the abductor pollicis brevis showed a marked fade with no posttetanic facilitation. The authors of the report[45] called this condition the "intermediate syndrome," meaning that it is intermediate between the acute cholinergic effects and the later, well-recognized delayed polyneuropathy. Consequently, the term intermediate syndrome, rather than type II signs, has been adopted.

Two additional cases of this syndrome were reported several years later; both patients required ventilatory support during the paralytic phase.[98] In another series, 29 of 90 patients with organophosphate poisoning had the intermediate syndrome.[99] Tetanic fade with no posttetanic facilitation was maximal between days 4 and 6, and the response to electrical stimulation had returned to normal by 8 to 10 days. The author suggested that a neuromuscular junction defect was responsible for the lesion. Other cases have since been reported[100–103] and in some, the weakness or paralysis lasted for days to weeks. Lack of early oxime therapy had been thought to contribute to the development of the syndrome,[104] but it has occurred with adequate amounts of oxime.[100,101,105] The cause of this neuromuscular dysfunction has not been elucidated, nor has an animal model been described. Intermediate syndrome may be related to the myopathy seen at the neuromuscular junction.

Nerve Agents

The occurrence of the intermediate syndrome following nerve agent exposure is not well characterized.[106] In one experiment, single fiber electromyography was used to examine the syndrome in volunteers exposed to a low level of sarin.[107] Significant, albeit small, changes in single fiber electromyography were observed at 3 hours and at 3 days following exposure. However, the electromyographic changes did not accompany clinical neuromuscular symptoms. The small changes observed were resolved when the volunteers were evaluated 2 years later.

Another study examined the delayed neurotoxic effects of repeated sarin inhalation in mice.[108] Female

Swiss mice received repeated whole-body exposure to 5 mg/m^3, 20 minutes daily for 10 days. The mice were evaluated daily for changes in gross behavior, and 4 days following the last exposure, the mice were examined histopathologically. The sarin-exposed mice exhibited muscular weakness in the limbs, twitching, and slight ataxis on the 14th day (4 days after the final exposure), despite clear anti-AChE signs. The histopathology results showed depressed neurotoxic esterase activity in the CNS and platelets, and axonal degeneration was observed in the spinal cord. The time frame of onset of the observed results is consistent with the intermediate syndrome, but could potentially have been OPIDN. The report did not follow mice past the 4th day postexposure, so it is unclear whether the symptoms would have resolved. Overall, there is limited information regarding the occurrence of the intermediate syndrome following nerve agent exposure.

Neuropsychiatric Effects

Many neuropsychiatric problems have been associated with single and repeated exposures to insecticides and nerve agents. In many cases these symptoms were studied shortly after the patients were exposed, and the duration of the problems was not noted. However, several studies examined the effects long after the acute insult. These effects include disturbances in memory, sleep, and vigilance; depression; posttraumatic stress disorder (PTSD); anxiety and irritability; and problems with information processing. In cases of exposure to nerve agents, the traumatic impact of experiencing a chemical warfare attack potentially confounds the evaluation of the long-term health effects of nerve agent exposure alone. Thus, whether caused by the direct effects of the chemical compound or by the event itself, the neuropsychological effects presented will still require attention by the attending clinician.

Insecticides

In 1961 Gershon and Shaw[109] described 16 patients with psychiatric problems who had been exposed to pesticides repeatedly over a 1.5- to 10-year period. Five were schizophrenic, seven were severely depressed, one was in a state of fugue, and all had impairment of memory and concentration. These conditions followed multiple symptomatic exposures to organophosphate insecticides, and the patients recovered within 6 to 12 months after the onset of their signs and symptoms. Because neuropsychiatric sequelae of organophosphate insecticides had not been widely recognized, the authors suggested that these sequelae might be more common than generally thought.

Gershon and Shaw's report was criticized[110,111] because no information on the exposure history was included; because few objective measures, either of mental status or of blood cholinesterase, were used; and because the conditions reported had not been reported in much larger series of patients exposed to organophosphate insecticides. Later studies failed to find evidence of thought disorders after pesticide exposure,[112,113] although diisopropyl fluorophosphate administration aggravated psychosis.[114] Less severe neuropsychiatric manifestations of organophosphate insecticide exposure, occurring either acutely or as sequelae, have been subsequently reported.

Durham et al[115] examined 187 individuals who were routinely involved in pesticide work (eg, crop dusting) for mental alertness. The groups were people with varying degrees of exposure to organic phosphorus pesticides and the control group were persons with no known previous exposure to these materials. The subjects were studied, using a complex reaction time, (*a*) at the time of maximal work with insecticides and (*b*) during "nonexposure" periods. Control subjects were studied at similar times. Both groups, subjects and controls, did better on tests during nonexposure periods, and both groups scored poorer during the higher risk periods. The performance of the exposed subjects improved during and after convalescence. The authors emphasized repeatedly that mental effects were not seen in the absence of clinical signs of poisoning. Problems with memory after insecticide exposure were reported by Gershon and Shaw[109] (the problems resolved 6 to 12 months after the acute exposure) and by Metcalf and Holmes[113] (the patients were studied more than a year after exposure). In the latter study, testing was performed to corroborate the report of memory deficit. Other reports have mentioned memory problems, but they provide few data.

Steenland et al[116] examined 128 agricultural workers who had been previously poisoned with at least one organophosphate pesticide between 1982 and 1990. Subjects were evaluated using a neurological test battery that included assessments of mood, motor speed, sustained visual attention, hand-eye coordination, simple reaction time, coding speed, visual memory, serial digit learning and memory, dexterity, and pursuit aiming. Total results showed consistent and significant impairments in mood scale, sustained visual attention, and coding speed. The researchers further performed a nerve conduction and vibrotactile sensitivity assessment of the same population, observing that nerve conductions were normal, but vibrotactile sensitivity was reduced. Together the results indicated that central and peripheral neurological damage related to organophosphorus pesticide poisoning likely occurred.

Anxiety, irritability, giddiness, tension, and restlessness persisting for months after exposure to insecticides were reported by Namba et al[117] and by Gershon and Shaw.[109] Both studies emphasized that these effects occurred only in patients who had demonstrated symptoms of exposure. Metcalf and Holmes[113] reported similar effects, but did not indicate their duration or the time after exposure that they occurred. Depression has been reported[117] from insecticide exposure immediately following the acute symptomatic exposure, but it did not persist. More prolonged (6 to 12 months) depression has been reported[109] after insecticide exposure. In contrast, Levin et al[112] found no evidence of depression using a structured interview and a depression inventory in asymptomatic workers with histories of chronic exposure. Sleep disturbances, such as excessive dreaming, nightmares, and insomnia, generally of relatively short duration (days to weeks), after insecticide exposure have also been reported.[113,117]

Psychomotor performance has been evaluated after exposure to insecticides. Rowntree et al[114] found that daily administration of an organophosphate compound caused slowness in thought and decreased performance speed. Metcalf and Holmes[113] noted slowed thinking and calculation in patients who had been exposed to insecticides more than a year previously. Difficulties in concentration and vigilance have been reported after insecticide exposure,[109,113,115,117,118] although some of the studies indicate marginal decreases, and others lack objective data (eg, Gershon and Shaw[109]). In all of the cases, the impairment occurred after an episode in which the patient had exhibited symptoms of exposure to the compound.

Tabershaw and Cooper[119] evaluated 87 patients who had been exposed to an organophosphate insecticide more than 3 years previously and who had had persistent complaints for over a 6-month period. The symptoms involved the visual, gastrointestinal, cardiorespiratory, and neuropsychiatric systems. In each instance, the complaint could be attributed to other problems; for example, several cases of visual blurring were due to presbyopia, a case of chronic abdominal pain was due to a peptic ulcer, and in one case, nervousness and tremors were due to chronic alcoholism.

In a more recent study, Rosenstock et al[120] examined 38 patients more than a year after their hospitalization for organophosphate insecticide exposure. Control subjects had also worked with organophosphate insecticides but had not had a symptomatic exposure. The poisoned group did significantly less well than the control group on tests assessing a wide variety of neuropsychological functions, including auditory attention, visual memory, visuomotor speed, sequencing and problem solving, and motor steadiness, reaction, and dexterity.

Nerve Agents

Bowers et al[68] reported that subjects had difficulty with memory for 24 hours after they were given VX, but had no evidence of major thought disorders. Other investigators[65] noted depression acutely after nerve agent exposure, but the depression did not persist. Sleep disturbances were also short-lived.[68,121,122] After exposure to VX, subjects had decreased performance on an arithmetic test, decreased reading comprehension, and decreased ability to play chess.[68] In some instances these performance decrements occurred before other signs of intoxication or in the absence of other signs. Impaired concentration and vigilance have been reported after nerve agent exposure.[121] These effects can persist for several weeks after symptomatic exposure to nerve agents.[123]

A report[122] of 297 cases of accidental exposure to nerve agent among manufacturing workers indicated that about 20% of the individuals had neuropsychiatric effects such as disturbed sleep, disturbance in mood, irritability, nervousness, disturbance in ability to think clearly, absentmindedness, fatigability, and lightheadedness. The duration of these effects was not indicated, but the report noted that supervisors and coworkers detected these effects when the casualties returned to work prematurely.

A single subject, a biochemist exposed to soman, was evaluated at 2 weeks, 4 months, and 6 months after exposure, using a psychiatric interview and a battery of psychological tests.[71] The person had been severely exposed, requiring ventilatory support for about 30 minutes. On initial testing, he had high scores on the hypochondriasis and hysteria scales on the Minnesota Multiphasic Personality Inventory; these improved on later testing. On the initial testing he did poorly on a visual retention task, word association proverbs, and an ink blot test. While taking the tests, he used delaying tactics, had difficulty generating verbal associations, and failed the harder proverbs. Results on the later tests were much improved and indicated full use of his intellectual faculties. In another case, a physician was exposed to sarin and required ventilatory support for more than 3 hours. Although psychiatric and psychological studies were not performed, he returned to work after recovery with no apparent problems.[72]

Although few data on the duration of these neuropsychiatric effects in people exist, evidence suggests that they are relatively short-lived (days or weeks). Because of the nature of their work, people handling

nerve agents in manufacturing plants, at depots, or in research and development facilities were relatively few in number, tended to remain in the same job for a long period, and comprised closely knit groups. Most were thoroughly familiar with the effects of nerve agents, and most knew their coworkers very well. If a worker did not seem "right," his coworker or supervisor recognized it.[122] A medical facility dedicated to the treatment of nerve agent casualties, with a staff experienced in this type of injury, was always available; workers were encouraged to use it, and supervisors were instructed to send employees who were not "normal" to the medical facility for evaluation.

One neuropsychiatric disorder that has been reported to persist following the Tokyo incident is PTSD. Soon after the events in the Tokyo subway in 1995, one hospital reported that as many as 60% of patients exhibited symptomatic PTSD up to 6 months after the initial event.[124] Furthermore, 32% of the victims were still feeling fear, 29% displayed insomnia, and 16% had flashbacks of their experience. Still others displayed depression (16%), irritability (16%), and persistent nightmares (10%). A 5-year follow-up of 34 patients involved in the Tokyo incident[125,126] examined serum cholesterol, uric acid, cholinesterase, and PTSD. From this group, eight patients (23%) developed PTSD following the event, and two were diagnosed with the disorder at the time of the assessment. Comorbidity of PTSD with other mental illness, including anxiety, agoraphobia, panic disorders, and severe depression, was also observed in the group that developed the disorder. Although no relationship of PTSD with cholesterol or uric acid was apparent, the disorder had a surprising relationship to serum cholinesterase. Relative to patients who did not develop PTSD, the patients who developed PTSD had lower serum cholinesterase both within 3 days of the attack and 5 years following the event. However, both groups had significantly reduced cholinesterase immediately following the attack versus the 5-year assessment; thus, the relationship of reduced cholinesterase and PTSD is not readily apparent.

Other studies show the development of PTSD with related neuropsychiatric symptoms in sarin-exposed patients following the Tokyo subway incident, but not all showed persistent decreased cholinesterase. A group of 18 male and female sarin patients were neurobehaviorally assessed 6 to 8 months following the terrorist incident.[127] Relative to matched controls, the sarin patients presented with significantly depressed cholinesterase activity at the time of hospital admission that had recovered by the time of the assessment. At the follow-up assessment the sarin patients showed significantly more psychiatric symptoms; fatigue; impaired Wechslar Adult Intelligence Scale digit symbol performance (a measure of motor persistence, sustained attention, response speed, and visuomotor coordination); and extended latencies for P300 auditory event-related and P100 visual brain-evoked potentials related to PTSD. The P300 evoked potential serves as a neural marker of the ability to allocate and sustain attention, and the P100 visual evoked potential is a marker for the conduction time from the retina to the visual cortex.

In summary, studies intended to examine the neuropsychiatric effects of organophosphate compounds vary in their adequacy, and in some instances the results are contradictory. Most studies agree, however, that acute neuropsychiatric effects result from exposure to both insecticides and nerve agents. These effects include inability to concentrate, memory problems, sleep disturbances, anxiety, irritability, depression, problems with information processing and psychomotor tasks, and potentially PTSD. With pesticides, these effects do not occur in the absence of the conventional signs of poisoning. The duration of these effects is less well studied. Some studies suggest that after exposure to insecticides, problems might persist for a year or longer, but supporting data are not always provided. The two reports of patients exposed to nerve agents and personal observation suggest that these effects are of shorter duration in this class of compounds.

Electroencephalographic Abnormalities

Insecticides and Other Organophosphates

Electroencephalographic abnormalities were reported in subjects given daily doses of diisopropyl fluorophosphate for 2 to 7 days.[128] These abnormalities consisted of faster frequencies, higher voltages, and occasional bursts of slow waves of high voltage at 3 to 6 Hz. Their severity was directly related to the degree of initial cholinesterase inhibition. The changes persisted for 3 to 4 weeks. Changes were noted in the electroencephalograms (EEGs) of 50 industrial and agricultural workers within 72 hours of accidental exposure to insecticides (both organophosphate and chlorinated hydrocarbons, on separate occasions), although the relationship to work history, blood cholinesterase, and exposure type, duration, and severity were not mentioned.[113]

Nerve Agents

In a patient severely intoxicated with sarin, an EEG (taken after the loss of consciousness but before the onset of convulsions) showed marked slowing, with bursts of high-voltage slow waves at 5 Hz in the temporofrontal leads. These abnormalities persisted for 6

days, after which no residual effects were noted.[121]

Because of the reports on insecticides and concern for employees working with or in the vicinity of nerve agents, the US government sponsored a series of studies[129–132] on the long-term effects of sarin exposure as seen in EEG examinations. In the first study, monkeys were dosed with sarin in one of two dose schedules: (1) a single large dose that produced convulsions or (2) a series of 10 weekly doses that caused no clinical effects. In the second study, workers who had had at least one documented exposure to sarin (signs, cholinesterase depression) more than a year before the study were evaluated. Control subjects were coworkers who had no possibility of organophosphate exposure.

In the nonhuman primates, animals from both dose schedules had increases in high-frequency beta activity a year after exposure. Spectral analysis of the EEGs of the humans showed increased beta activity in the sarin-exposed population compared to the control population. Visual reading of the records suggested decreased amounts of alpha and increased amounts of slow delta and theta activity in the exposed group. Increased amounts of rapid-eye movement sleep in the exposed group were also found. Individual records could not be categorized. The investigators noted that the relationship between these changes and alterations in brain function was not known.

Toxicological Studies on Nerve Agents

The effects of exposure to nerve agents on a chronic or subchronic basis were reported in two studies on animals. In a two-part, 90-day study[133,134] of subchronic exposure, rats were given one of three doses of tabun or soman 5 days per week by gavage. At the end of the study, no abnormalities were found on gross or histological examination of tissue. In a study[135] of chronic exposure to sarin, dogs received a Ct of 10 mg•min/m^3 of sarin over a 6-month period. Some animals were dosed 5 days per week, and some were dosed 7 days per week. No tissue abnormalities that could be attributed to the agent were noted on gross or microscopic examination. Several of the male animals were bred after the exposure and the pups were normal. In studies[136–139] in which tabun, sarin, and soman were given to hens in single or multiple doses, in amounts maximally tolerated with the coadministration of atropine, no evidence of polyneuropathy was noted clinically or on microscopic examination.

Sarin and soman were deemed not mutagenic after they were studied using Ames *Salmonella*, mouse lymphoma, and Chinese hamster ovary cell systems.[140] Tabun was found to be weakly mutagenic in the mouse lymphoma cell test,[141] Chinese hamster ovary system,[142] and Ames bacterial system.[143]

CYANIDE

Cyanide is a lethal poison that can produce death within 10 minutes. Cyanide compounds are used extensively in industry and are present in the environment from many sources. Humans can be exposed to cyanide by ingestion, inhalation, or injection. However, humans produce minute quantities of cyanide for normal metabolic processes and also possess a limited capability to detoxify ingested or inhaled cyanide. This review of cyanide long-term effects differentiates the long-term outcomes of a high-level acute exposure as compared to a long-term exposure.

Physiology

Cyanide is a potent inhibitor of aerobic metabolism through interruption of oxygen binding within mitochondrial cytochrome oxidase. Tissues that depend greatly on aerobic respiration, such as cardiac muscle and nerve tissue, are most affected. Besides these effects and those on many other enzymes, cyanide is also cardiotoxic and neurotoxic.[144] Much of the CNS toxicity of cyanide appears to be related to direct toxicity on neurons with glutamic acid receptors. Cyanide-induced striatal degeneration is mediated by short-term, high-level exposures affecting *N*-methyl D-aspartate glutamate receptors.[145] Neuronal degeneration based upon long-term exposure to cyanide and its metabolites appears to be mediated through α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid glutamate receptors.[146]

Cyanide detoxification is extensively reviewed in Chapter 11, Cyanide Poisoning, though it is important to note that the primary biological means of detoxification is the conversion of cyanide to thiocyanate through a sulphurtransferase reaction followed by urinary excretion.

Long-Term Effects of an Acute Insult

Outcomes of severe cyanide intoxications are highly variable. Many victims of moderate to severe exposures who recover have no sequelae. For others, the outcome often is a factor of timely diagnosis and effective treatment.

A chemical company that produces large quantities of cyanide for plastic manufacturing reported the results of eleven cyanide inhalations and two cutaneous exposures. The cases varied in severity of symptoms

from headache and dizziness to death (although only one person died, and this individual was in extremis when found). All individuals in the report who had vital signs at the time of discovery recovered. Most of the victims inhaled cyanide fumes for 30 to 90 seconds and became unconscious with irregular respirations or apnea. All these patients received supportive care of bagged oxygen and amyl nitrite within 5 minutes. One surviving patient required intravenous antidotes as well as amyl nitrite, and the rest recovered with amyl nitrite and artificial ventilation alone. Nearly all the patients recovered quickly, and some were even sent back to work after a few hours of observation. No long-term effects were reported. These cases demonstrate the efficacy of simple field treatment if implemented within a few minutes of exposure. It is noteworthy that patients who remained conscious after inhalation of cyanide recovered with supplemental oxygen and no antidotes.[147]

Medical reports from severe ingestions include various outcomes. Many patients responded to treatment and experienced complete recovery. Other outcomes were difficult to discern because the patients may have developed global deficits from prolonged hypoxia. In some severe casualties, a distinct pattern of neurological impairment occurred. The basal ganglia appeared to be particularly vulnerable to insult from cyanide, with frequent involvement of the globus pallidus and putamen.[148] Symptoms reported were parkinsonian, with bradykinesia, shuffling gait, rigidity, and other symptoms resembling a generalized dystonia. Cognitive function sometimes remained intact.[149] In all cases with long term sequelae, the patients experienced significant delays of 30 minutes to hours before antidote administration. (There are several excellent case examples in Chapter 11, Cyanide Poisoning.)

Long-Term Exposure

Long-term exposure to cyanide contributes to a number of conditions, although the different diseases usually have several features in common. First, they are primarily neurological diseases. Second, they involved prolonged exposures to cyanide-containing food or medication. Third, those affected tend to subsist on a monotonous diet with insufficient protein.

The most common dietary exposure is bitter cassava root, *Manihot esculenta* Crantz, which is widely consumed in the tropics and sub-Saharan Africa, where it ranks fourth in nutritional importance after rice, wheat, and maize. Cassava is a staple during times of famine because it can grow in poor soil and climate conditions. Cassava's cyanogenicity confers immunity to pests. Procedures such as prolonged soaking, smashing, or boiling are necessary to remove cyanogenic compounds such as linamarin. Fresh cassava roots can contain up to 1,500 mg hydrogen cyanide equivalent per kilogram.[145] Acute intoxications, even death, have resulted from consumption of raw cassava, though long-term exposures from incompletely processed cassava are more likely.

Konzo ("tied legs") is a form of spastic paraparesis found among poor rural populations of central and east Africa who primarily consume cassava. It affects individuals of all ages. Konzo is symmetrical, isolated, and permanent. It is associated with sensations of heaviness and weakness in legs that can cause the inability to stand. It is often present in entire families and varies in severity from a mild toe-scissor gait, to requiring a walking stick, and to the point where walking is not possible. Those at risk for konzo have ankle clonus and lower extremity hyperreflexia.[150] Konzo is also associated with optic neuropathy.[151] Individuals with konzo are noted to have very high levels of urinary thiocyanate. They are also protein deficient, with a great deal of ingested amino acid sulphur diverting to cyanide detoxification.[152] Linamarin has been identified as a specific toxic factor in this disease. It is also thought that overwhelmed detoxification mechanisms and an abrupt increase in metabolites over their chronic levels lead to the sudden clinical presentation of konzo.[153]

Tropical ataxic neuropathy is a distinct cyanide-related disease with several other names that is classically associated with prisoners of war or middle-aged and elderly persons in southwestern Nigeria. It is a polyneuropathy associated with bilateral optic atrophy, bilateral neurosensory deafness, and sensory gait ataxia. This condition was widespread in Nigeria until an improved diet resulting from the 1970s oil boom relegated this condition to rural areas.[154] Tropical ataxic neuropathy is a gradual onset, permanent condition associated thiocyanate, cyanate, and a monotonous cassava diet.[155]

Smokers are known to have blood cyanide levels significantly higher than the nonsmoking population.[156] Tobacco amblyopia is caused by chronic cyanide levels sometimes coupled with malnutrition and alcoholism. Symptoms are loss of color perception and decreased vision, which is often recoverable after discontinuation of smoking or even administration of cyanide antidotes. This once-common syndrome has become rare in the United States.[157]

Another cyanide-related disorder is Leber hereditary optic neuropathy (LHON). LHON, first described in 1871, is a maternally inherited disease of highly variable penetrance that impairs oxidative phosphorylation. LHON is the model disease for mutations of the mitrochondrial genome. The disease is heteroplasmic,

usually requiring more than 60% mutant genes for symptoms to present. Patients with LHON are normal until the sudden onset of blindness between the ages of 15 and 35.[158] The stressor leading to cell death of the highly aerobic optic nerve is the elevated blood cyanide level associated with smoking and the associated blood cyanide level.[159]

Given the likely acute high-level exposure expected in a military environment, it is reasonable to ask whether cyanide exposure can lead to blindness in some individuals. This is theoretically possible in the small fragment of the population with LHON mutations, although no cases have been reported. There is only one case of blindness from acute cyanide poisoning in the literature, a temporary case caused by a sodium nitroprusside overdose.[160]

Cyanide can also be responsible for some cases of goiter. Elevated levels of thiocyanate as well as thyroid abnormalities have been documented in individuals on cyanogenic food diets and those in industries with chronic exposures such as electroplating.[161] Thiocyanate prevents uptake of iodine into the thyroid gland.[162]

Patients with chronic renal failure who smoke have been known to develop a condition known as uremic neuropathy, a result of the accumulation of thiocyanate, the major detoxification metabolite of cyanide. In these patients, thiocyanate cannot be removed from the body, even with dialysis. Treatment involves administration of hydroxocobalamin antidote, which uses a different chemical pathway.[163]

Several conditions were previously thought to be associated with cyanide, including lathyrism, a neurological disorder associated with grass pea ingestion. Subacute combined degeneration of the spinal cord, attributed to cyanide in the past, is now well known to be related to vitamin B12 metabolism.

In summary, the long-term effects of cyanide exposure are highly variable. Severe exposures and cases with delayed treatment may manifest in a Parkinsonian akinetic syndrome. Long-term exposure to cyanide is likely in areas where cassava is the staple food and represents a likely risk to future prisoners of war in these areas. Long-term cyanide exposure combined with poor protein intake leads to neuromotor and neurosensory disorders. Smoking represents a chronic cyanide exposure that may lead to permanent blindness in rare individuals. Most importantly, the majority of cyanide-exposed individuals who receive prompt treatment may expect no long-term sequelae following an acute cyanide exposure. This fact emphasizes the importance of prompt casualty care.

TOXIC INHALATION INJURY

The pulmonary agents are absorbed almost exclusively by inhalation. They readily penetrate to the level of the respiratory bronchioles and alveoli, that is, to the peripheral compartment of the respiratory tree. However, most of these agents are essentially consumed by reactions occurring at the alveolar-capillary membrane, or more proximally in the respiratory tract, and are not systemically distributed to a clinically significant extent.

Inhalation of selected organohalides, oxides of nitrogen, and other compounds can result in varying degrees of pulmonary edema, usually after a symptom-free period that varies in duration with the amount inhaled. Chemically induced acute lung injury by these agents involves a permeability defect in the blood–air barrier (the alveolar-capillary membrane); however, the precise mechanisms of toxicity remain an enigma. The United States produces over a billion pounds of phosgene per year for industrial uses; however, it is not stockpiled for military use.

Perfluoroisobutylene (PFIB) is a toxic pyrolysis product of tetrafluoroethylene polymers encountered in military materiel (eg, Teflon [DuPont, Wilmington, Del] found in the interior of many military vehicles). The oxides of nitrogen are components of blast weapons or may be toxic decomposition products. Smokes (eg, HC) contain toxic compounds that cause the same effects as phosgene.[164] The long-term health effects of phosgene exposure also apply to casualties from agents such as PFIB and oxides of nitrogen.[165]

Phosgene

Phosgene produces pulmonary edema following a clinical latent period of variable length that depends primarily on the intensity of exposure (ie, the C*t*), but also partly on the physical activity of the exposed individual. After the latent period, the patient experiences worsening respiratory distress that at first is unaccompanied by objectively verifiable signs of pulmonary damage, but may progress relentlessly to pulmonary edema and death.

During the time preceding the appearance of shortness of breath, individuals exposed to particularly high concentrations of organohalides may report symptoms associated with mucous membrane irritation. Exposure to large quantities of phosgene may irritate moist mucous membranes, presumably because of the generation of hydrochloric acid from the hydrolysis of phosgene. Transient burning sensation in the eyes with

lacrimation and chemical conjunctivitis may coexist with mild, early onset cough and a substernal ache with a sensation of pressure. Irritation of the larynx by very large concentrations of the agent may lead to sudden laryngeal spasm and death.

A clinical latent period during which the patient is asymptomatic may follow low C*t* exposure or the transient irritation associated with substantial phosgene exposure. This asymptomatic period may persist up to 24 hours after organohalide inhalation. The duration of the latent period is shorter following a high dose and is shortened by physical exertion following exposure.

The most prominent symptom following the clinical latent period is dyspnea, perceived as shortness of breath, with or without chest tightness. These sensations reflect hypoxemia, increased ventilatory drive, and decreased lung compliance, all of which result from the accumulation of fluid in the pulmonary interstitial and peripheral airways. Fine crackles can be heard at the lung bases, but these may not be clearly audible unless auscultation is conducted after a forced expiration. Later, auscultation reveals coarse crackles and rales in all lung fields, and increasing quantities of thin, watery secretions are noted. The buildup of fluid in the lungs has two clinically pertinent effects. First, developing pulmonary edema interferes with oxygen delivery to alveolar capillaries and may lead to hypoxemia, and if a sufficient percentage of hemoglobin is unoxygenated, cyanosis will become apparent. Second, the sequestration of plasma-derived fluid (up to 1 L per hour) in the lungs may lead to hypovolemia and hypotension, interfering with oxygen delivery to the brain, kidneys, and other crucial organs. Death results from respiratory failure, hypoxemia, hypovolemia, or a combination of these factors. Hypoxia and hypotension may progress particularly rapidly, which suggests a poor prognosis. The development of symptoms and signs of pulmonary edema within 4 hours of exposure is an especially accurate indicator of a poor prognosis; in the absence of immediately available intensive medical support, such patients are at high risk of death. Complications include infection of damaged lungs and delayed deaths following such respiratory infections.[164] Several studies sponsored by the Veterans Administration using animals and humans reported that after phosgene exposure pulmonary edema appeared very early.[166]

In July 1920, Winternitz's[167] report on experimental work with dogs revealed acute changes in the cardiorespiratory system following exposure to lethal concentrations of phosgene. The upper portion of the respiratory tract was not affected, but the alveoli of the lungs and the finer bronchi gave evidence of congestion, inflammation, and edema. The inflammatory reaction following phosgene exposure resulted in congestion of the bronchial and spread into the surrounding air cells, indicative of an early bronchopneumonia with a marked edema of the lungs. Dilatation, reflex bronchiolar spasm, and plugging of the bronchiols with exudates led to patches of atelectasis and emphysema. A substantial amount of fibrin on alveolar walls, crossing and obstructing the capillaries, led to resistance in the pulmonary circulation, with a consequent dilatation of the right heart. In the dogs, damage occurred principally in the respiratory tract, and lesions varied according to the length of survival after the exposure. Initial pulmonary edema associated with congestion reached a maximum intensity toward the end of the first 24 hours and gradually disappeared in animals surviving 10 days or longer. With the edema, there was an associated inflammatory exudation of fibrin and leucocytes. This cellular exudate was found especially in the finer bronchioles and extended into the alveolar tissue. It was suggestive of a lobular pneumonia. The pneumonia was frequently complicated by necrotization of the walls of the bronchioles, which also involved the adjacent alveoli and resulted in abscess formation. In some cases, although the inflammatory process was succesesfully overcome, an obliterative bronchiolitis resulted.

In the exposed dogs, the pathology was localized to the trachea and bronchi. The epithelium of the trachea and larger bronchi was damaged, while the smaller bronchi and bronchioles were the most seriously affected. In addition to changes in the mucosa, there were contractions, distortions of the bronchioles, and more or less obliteration of the lumina. All this led to mechanical disturbance in the air sacs, with resting atelectasis and emphysema.

The Veterans Administration conducted a study reviewing the histories of 10 veterans who had been gassed with phosgene and showed evidence of physical effects a number of years later.[166] This historical study revealed that chronic bronchitis was the most frequent long-term effect noted. Emphysema was noted in three of the veterans, pulmonary fibrosis was noted in two, chronic-active pulmonary tuberculosis was found in one case, and bronchial asthma was found in another. This study also revealed that the symptoms of the pulmonary disabilities were observed immediately after the phosgene gas exposure and continued to be the causative factor the long-term pulmonary effects at the time of the study.[166]

According to the Veterans Administration, the following pathological changes were noted in soldiers who died following phosgene gas exposure[166]:

- Pulmonary edema, usually very marked, occurred. The pleural cavities generally contained an excess of fluid.
- The lungs, upon removal from the thorax, were voluminous, heavy, and bluish-red in color; occasionally, petechial hemorrhages and alternating patches of emphysema and collapsed lung tissue were noted.
- Section of lungs showed an exudation of frothy fluid from the cut surface.
- Irregular, alternating areas of edema and acute emphysema were noted.
- The trachea, bronchi, and bronchiole were generally filled with thin, yellowish, serosanguineous fluid.
- There was little or no inflammatory change in the larynx, trachea, and bronchi.
- The veins were engorged.
- The heart, especially on the right side, was dilated.
- Petechial hemorrhages were often found beneath the endocardium.
- The pericardial fluid increased in amount.
- The abdominal viscera showed the presence of generalized venous engorgement and congestion.
- The meninges of the brain were congested.

Methyl Isocyanate

In December 1984, in Bhopal, India, a massive leak of methyl isocyanate resulted from operational and equipment malfunctions in a pesticide plant. Many thousands of residents of the city, most in proximity to the plant, suffered sublethal and lethal respiratory injuries, the expected consequences of high-level exposure to this type of potent irritant chemical vapor. Animal toxicological information was limited prior to the accident, but has since confirmed that the lung is the major target of these lethal injuries, invariably with pulmonary edema. Early concerns about acute cyanide intoxication were not supported by subsequent scientific inquiry. Superficial corneal erosions did not result in permanent eye injury. The primary unresolved (and perhaps irresolvable) medical issue is the incidence and determinants of long-term respiratory injury in the survivors. Limited available evidence suggests that chronic damage, when present, is or resembles fibrosing bronchiolitis obliterans, the expected consequence when permanent injury results from acute, high-level irritant gas exposure. Definition of the follow-up population is uncertain, and exposure information is lacking. Dose-response relationships are not likely to emerge from follow-up studies.[168]

Perfluoroisobutylene

PFIB primarily affects the peripheral compartment of the pulmonary system. Although animal studies occasionally report disseminated intravascular coagulation and other organ involvement, these effects only occur with substantial pulmonary injury to the peripheral compartment of the pulmonary system, suggesting that systemic hypoxia is a major factor.[169] No human studies have reported organ involvement other than the respiratory system. Pathological data on acute human exposure to PFIB are not available; however, pathological data on animals show both histological and ultramicroscopic changes occurring within 5 minutes of exposure.[170] Interstitial edema with alveolar fibrin deposition progresses rapidly over 24 hours, and then gradually subsides until the patient is fully recovered. At 72 hours, a type II pneumocyte hyperplasia is seen (interpreted as consistent with known reparative processes). Some long-term pathological changes in animals have been noted but most animal studies do not identify such long-term effects.[171] Human long-term pathological data are available for only one reported case: a 50-year-old woman who experienced approximately 40 episodes of polymer fume fever—typically occurring from smoking contaminated cigarettes. Eighteen months after her last episode, progressive exercise dyspnea was noted. A cardiopulmonary physical examination, chest radiograph, and arterial blood gas were all normal. Pulmonary function testing supported a provisional diagnosis of alveolar capillary block syndrome (decreased diffusion capacity of carbon monoxide, increased exercise alveolar-arterial oxygen gradient, and minimal airway disease). Death occurred from an unrelated cause. The autopsy provided histological evidence of moderate interstitial fibrosis with minimal chronic inflammatory cell infiltrate.[172] Only two human deaths from pyrolysis products of polymerized organofluorides have been reported.[173,174]

Oxides of Nitrogen

Inhalation of nitric oxide causes the formation of methemoglobin. Inhalation of nitrogen dioxide results in the formation of nitrite, which leads to a fall in blood pressure, production of methemoglobin, and cellular hypoxia, which causes rapid onset pulmonary edema.

The clinical response to oxides of nitrogen exposure is essentially triphasic. In phase 1, symptoms appear more or less quickly, depending on the intensity of exposure. With a low dose, initial eye irritation, throat tightness, chest tightness, cough, and mild nausea may appear. Once the casualty is removed from the source of exposure, these symptoms disappear spontaneously over the next 24 hours. However, at 24 to 36 hours

postexposure, a particularly severe respiratory symptom complex may appear suddenly; exertion seems to be a prominent precipitating factor. There may be severe cough, dyspnea, and rapid onset of pulmonary edema. If the patient survives this stage, spontaneous remission occurs within 48 to 72 hours postexposure. More intense exposures produce a relatively rapid onset of acute bronchiolitis with severe cough, dyspnea, and weakness, without the above-mentioned latent period. Again, spontaneous remission occurs at approximately 3 to 4 days postexposure.[175]

Phase 2 is a relatively asymptomatic period lasting approximately 2 to 5 weeks. A mild residual cough with malaise and perhaps minimal shortness of breath may occur, as well as a sense of weakness that may progress. The chest radiograph, however, typically is clear. In phase 3, symptoms may recur 3 to 6 weeks after the initial exposure. Severe cough, fever, chills, dyspnea, and cyanosis may develop. Crackles are identified on physical examination of the lung. The polymorphonuclear white blood cell count is elevated, and the partial pressure of carbon dioxide may be elevated as well.[176] The chest radiograph demonstrates diffuse, scattered, fluffy nodules of various sizes, which may become confluent progressively, with a butterfly pulmonary edema pattern and a prominent acinar component. At this point, pathological study demonstrates classic bronchiolitis fibrosis obliterans, which may clear spontaneously or may progress to severe, occasionally lethal respiratory failure. The fluffy nodular changes noted in the chest radiograph typically show no clinical improvement. Pulmonary function testing may show long-term persistence of airways obstruction.[177–179]

Zinc Oxide

Hexachloroethane (HC) smoke, a mixture of equal amounts of HC and zinc oxide with additional ingredients, is a toxic military smoke and obscurant. HC's toxicity is attributed to the irritating effects of zinc chloride. Most likely, carbon monoxide, phosgene, hexachloroethane, and other products contribute to the observed respiratory effects. The damage to the pulmonary system is confined largely to the upper respiratory tract, where zinc chloride acts much like a corrosive irritant. Studies reveal that HC exposure can produce a gradual decrease in total lung capacity, vital capacity, and diffusion capacity of carbon monoxide. HC is associated with the presence of pulmonary edema, increased airway resistance, and decreased compliance. When HC smoke exposure is discontinued, the pulmonary changes are reversible in all but 10% to 20% of those effected, who could develop pulmonary fibrotic changes.[180]

In a study by Conner et al[181] performed with guinea pigs, exposure to ultrafine HC particles (0.05 μm) in increasing degrees was associated with a dose-response elevation in protein, neutrophils, and angiotensin-converting enzyme found in lavage fluid. A direct relationship also was observed with alkaline phosphatase, acid phosphatase, and lactate dehydrogenase in lavage fluid. Centriacinar inflammation was seen histologically, indicating evidence of pulmonary damage. A study by Marrs et al[182] involving mice, rats, and guinea pigs demonstrated a positive association of alveologenic carcinoma in a dose-response trend to HC smoke, as well as a variety of inflammatory changes. The article states that hexachloroethane and zinc, as well as carbon tetrachloride (which may be present in HC smoke), may be animal carcinogens in certain circumstances. This raises the suspicion of HC as a potential carcinogen.

Metal fume fever is a well-documented acute disease induced by intense inhalation of metal oxides, especially zinc oxide. The exact pathology is not understood, but the clinical syndrome is well described and has been studied at length. A study by Kuschner et al[183] on human volunteers showed that pulmonary cytokines such as tumor necrosis factor, interleukin 6, and interleukin 8 may play important initial roles in mediating metal fume fever. Prolonged exposures or exposures to very high doses of HC may result in sudden early collapse and death, possible as a result of laryngeal edema or glottal spasm. If severe exposure does not kill the individual immediately, hemorrhagic ulceration of the upper airway may occur, with paroxysmal cough and bloody secretions. Death may occur within hours secondary to an acute tracheobronchitis.

Most individuals with HC inhalation injuries progress to complete recovery. Of exposed individuals, 10% to 20% develop fibrotic pulmonary changes. Distinguishing between those who will recover and those who will not is difficult, because both groups make an early clinical recovery.

SUMMARY

A wide variety of chemical agents and industrial products are associated with long-term health consequences after an acute insult. Others are known to be harmful with prolonged low-level exposure. The linkage between these associations is sometimes tenuous given the limitations of retrospective studies and case reports up to 90 years old. Research laboratory efforts and future case reports will continue

to strengthen the understanding of these effects. In the meantime, the existing knowledge base provides clinicians sufficient reason to monitor for these possible outcomes and apply proactive surveillance to individuals working with these chemicals on a daily basis.

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