Chapter 5

NERVE AGENTS

FREDERICK R. SIDELL, M.D.*

Formerly, Chief, Chemical Casualty Care Office, and Director, Medical Management of Chemical Casualties Course, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010-5425; currently, Chemical Casualty Consultant, 14 Brooks Road, Bel Air, Maryland 21014

INTRODUCTION

Nerve agents are extremely toxic chemicals that were first developed in secrecy before and during World War II primarily for military use. Related substances are used in medicine, in pharmacology, and for other purposes, such as insecticides, but they lack the potency of the military agents. Much of the basic knowledge about the clinical effects of nerve agents comes from research performed in the decades immediately following World War II.

The military stockpiles of several major powers are known to include nerve agents, and the armamentaria of other countries are thought to contain them as well (see Chapter 4, The Chemical Warfare Threat and the Military Healthcare Provider). Because of the possibility of nerve agent use in future conflicts, military medical personnel should have some knowledge of these agents, their effects, and the proper therapy for treating casualties.

HISTORY

Possibly the earliest recorded use of a substance that works, like nerve agents, by inhibiting cholinesterase (ChE) is by native tribesmen of western Africa who used the Calabar bean as an "ordeal poison" in witchcraft trials.[1,2] An extract, "the elixir of the Calabar bean," was later used medicinally,[3] and in 1864, the active principle was isolated by Jobst and Hesse and called physostigmine.[1] Vee and Leven independently isolated this same substance in 1865 and named it eserine,[1] hence its dual nomenclature.

The first organophosphorus ChE inhibitor was probably tetraethyl pyrophosphate (TEPP), synthesized by Wurtz and tasted (with no ill results) by Clermont in 1854.[4] During the next 80 years, chemists (such as Michaelis, Arbusow, and Nylen) made numerous advances in organophosphorus chemistry, but generally they did not realize the toxicity of the substances with which they were working.[4]

In the early 1930s, interest in both physostigmine-type (reversible) and organophosphorus-type (irreversible) ChE inhibitors increased. (The terms "reversible" and "irreversible" refer to the duration of binding of the compound with the enzyme ChE; see the Mechanism of Action section below.) The reversible type, most of which are carbamates, were developed for treating conditions such as intestinal atony, myasthenia gravis, and glaucoma; for example, treating gastric atony with neostigmine was described in 1931.[1]

Five organophosphorus compounds are generally regarded as nerve agents. They are commonly known as tabun (North Atlantic Treaty Organization [NATO] military designation, GA), sarin (GB), and soman (GD); and GF and VX (also NATO military designations; these compounds have no common names). The agents in the "G" series allegedly were given the code letter G because they originated in Germany; the "V" allegedly stands for venomous. GF is an old agent, previously discarded by the United States as being of no interest. During the Persian Gulf War, it was believed that Iraq might have GF in its arsenal; however, interest has waned again and GF has retreated to obscurity.

Lange and Krueger reported on the marked potency of organophosphorus compounds in 1932 after noting the effects of the vapors of dimethyl and diethyl phosphorofluoridate on themselves.[1,4] Shortly thereafter, the German company I. G. Farbenindustrie developed an interest in organophosphorus compounds as insecticides. On 23 December 1936, Gerhard Schrader, who headed the company's research effort, synthesized what today is known as tabun.[5,6] Like Lange and Krueger, he noted the toxicity (miosis and discomfort) of the vapors of the substance in himself.

Over a year later, Schrader synthesized a second organophosphorus compound and named it sarin in honor of those who were instrumental in its development and production: *S*chrader, *A*mbros, *R*udriger, and van der L*in*de.[5] Because the German Ministry of Defense required that substances passing certain toxicity tests be submitted to the government for further investigation, these compounds were examined for possible military use.

The potential of tabun and sarin as weapons was soon realized. A large production facility was built in Dyhernfurth and production of tabun was begun in 1942.[5,6] Sarin was also produced in Dyhernfurth and possibly at another plant in Falkenhagen.[6] Late in World War II, Soviet troops captured the Dyhernfurth facility (then in Germany, now in Poland), dismantled it, and moved it, along with key personnel, to the former Soviet Union, where production of the agents commenced in 1946.[6]

About 10,000 to 30,000 tons of tabun and smaller quantities of sarin were produced and put into munitions by the Germans during World War II, but these weapons were never used.[6] Why they were not remains a matter of conjecture.

In the waning days of World War II, troops of the United States and the United Kingdom captured some of these munitions, which were being stored at Raubkammer, a German testing facility. The munitions, which contained an agent unknown to scientists in the United Kingdom and the United States, were taken to the two countries for examination. Over a single weekend, a small group of scientists at the U.K. Chemical Defence Establishment, working despite miosis caused by accidental exposure to the agent vapor, elucidated the pharmacology and toxicity of tabun and documented the antidotal activity of atropine.[7]

Thus, during the latter part of World War II, Germany possessed chemical weapons against which its foes had little protection and no antidotes. Use of these weapons probably would have been devastating and might have altered the outcome of that conflict. The Germans had tested nerve agents on inmates of concentration camps, not only to investigate their intoxicating effects but also to develop antidotes.[8] Many casualties, including some fatalities, were reported among the plant workers at Dyhernfurth; the medical staff there eventually developed antidotal compounds.[5] The Allies were unaware of these German experiments until the close of the war, months after the initial U.K. studies.[7]

Soman was synthesized in 1944 by Richard Kuhn of Germany, again in a search for insecticides.[6] Small amounts were produced, but development had not proceeded far by the end of the war. The nerve agent VX was first synthesized by an industrial concern in the United Kingdom in the early 1950s[6] and was given to the United States for military development.

Other potential nerve agents were synthesized by scientists in the United States and United Kingdom but were not developed for military use. For example, GF, which may have been first synthesized about 1949 by a chemist in another country in the search for other nerve agents, was studied in both the United States and the United Kingdom. It was then discarded for reasons that are not entirely clear. Possible explanations are that it was too expensive to manufacture or that there was no perceived need for an agent with its properties. The manufacturing process for GF is apparently similar to that for GB. During the Persian Gulf War (1990–1991), Iraq was believed to have switched from the manufacture of GB to the manufacture of GF when the precursors of GB, but not those of GF, were embargoed.

The United States began to produce sarin in the early 1950s, and VX in the early 1960s, for potential military use; production continued for about a decade.[6] The U.S. munitions inventory today contains these two nerve agents in 30- to 45-year-old M55 rockets; land mines; 105-mm, 155-mm, and 8-in. projectiles; 500-lb and 750-lb bombs; wet-eye bombs (one of a family of "eye" bombs, which has liquid chemical [wet] contents); spray tanks; and bulk containers.[9] These munitions are stored at six depots within the continental United States (CONUS) and one outside the continent; the locations of these depots are public knowledge.[10] The six CONUS depots are near Tooelle, Utah; Umatilla, Oregon; Anniston, Alabama; Pine Bluff, Arkansas; Newport, Indiana; and Richmond, Kentucky; the seventh depot is on Johnston Island in the Pacific Ocean.

Sarin has also been used in terrorist attacks. In June 1994, members of a Japanese cult released sarin in an apartment complex in Matsumoto, Japan. Although there were almost 300 casualties, including 7 dead, this event was not well publicized. On 20 March 1995, sarin was released on Tokyo subways. More than 5,500 people sought medical care; about 4,000 had no effects from the agent but 12 casualties died. This incident required a major expenditure of medical resources to triage and care for the casualties. (Also see Chapter 1, Overview: Defense Against the Effects of Chemical and Biological Warfare Agents).

PHARMACOLOGY OF CHOLINESTERASE INHIBITORS

Cholinesterase in Tissue

Nerve agents are compounds that exert their biological effects by inhibition of the enzyme acetylcholinesterase (AChE), according to the current, widely accepted explanation. Some other compounds cause similar effects by the same mechanism and, in a broad sense, can also be considered nerve agents.

Acetylcholinesterase belongs to the class of enzymes called esterases, which catalyze the hydrolysis of esters. ChEs, the class of esterases to which AChE belongs, have high affinities for the esters of choline. Although there are several types of cho-

line esters, acetylcholine (ACh), the neurotransmitter of the cholinergic portion of the nervous system, is most relevant to nerve agent activity.

The enzyme AChE, found at the receptor sites of tissue innervated by the cholinergic nervous system, hydrolyzes ACh very rapidly: it has one of the highest enzyme turnover numbers (number of molecules of substrate that it turns over per unit time) known.[11] A similar enzyme having ACh as its preferred substrate is found in or on erythrocytes (red blood cells, RBCs) and is known as erythrocyte, or true, ChE (RBC-ChE). Butyrocholinesterase (BuChE, also known as serum or plasma cholinesterase, and as pseudocholinesterase), another enzyme of the ChE family, has butyrylcholine as its preferred substrate. Butyrylcholine is present in plasma or serum and in some tissues. BuChE and RBC-ChE are discussed in the Blood Cholinesterases section below.

Cholinesterase-Inhibiting Compounds

Most ChE-inhibiting compounds are either carbamates or organophosphorus compounds. Among the carbamates is physostigmine (eserine; elixir of the Calabar bean), which has been used in medicine for more than a century.[3] Neostigmine (Prostigmin, manufactured by ICN Pharmaceuticals, Costa Mesa, Calif.) was developed in the early 1930s for management of myasthenia gravis; ambenonium was developed later for this same purpose. Pyridostigmine bromide (Mestinon, manufactured by ICN Pharmaceuticals, Costa Mesa, Calif.) has been used for decades for the management of myasthenia gravis. The military of the United States and several other nations also field pyridostigmine bromide (manufactured by Phillips Duphar, Holland), known as PB or NAPP (nerve agent pyridostigmine pretreatment), as a pretreatment, or antidote-enhancing substance, to be used before exposure to certain nerve agents (see Chapter 6, Pretreatment for Nerve Agent Exposure). Today these carbamates are mainly used for treating glaucoma and myasthenia gravis. Other carbamates, such as Sevin (carbaryl, manufactured by Techne, St. Joseph, Mo.), are used as insecticides.

Most commonly used insecticides contain either a carbamate or an organophosphorus compound. The organophosphorus insecticide malathion has replaced parathion, which was first synthesized in the 1940s. The organophosphorus compound diisopropyl phosphorofluoridate (DFP) was synthesized before World War II and studied by Allied scientists before and during the war, but was rejected for use as a military agent. For a period of time, this compound was used topically for treatment of glaucoma but later was rejected as unsuitable because it was found to produce cataracts. It has been widely used in pharmacology as an investigational agent.

Mechanism of Action

Nerve agents inhibit ChE, which then cannot hydrolyze ACh. This classic explanation of nerve agent poisoning holds that the intoxicating effects are due to the excess endogenous ACh. This explanation, however, may not account for all nerve agent effects.

Research suggests that other nerve agent actions may contribute to toxicity. For example, ChE inhibitors inhibit enzymes other than ChE; the effect of this inhibition of additional enzymes on nerve agent toxicity may be significant.[12] Concentrations of ChE inhibitors that are severalfold higher than lethal concentrations produce direct effects on receptor sites by blocking conductance through the ion channel or by acting as agonists at the channel complex.[13] While these findings offer hope that better means of therapy will be developed in the future, their relevance to clinical effects is not clear at this time.

A detailed discussion of the chemistry of ChE inhibition is beyond the scope of this chapter and can be found in most textbooks of pharmacology (eg, see Koelle[11]). The relevant aspects are summarized here.

The efferents of the human nervous system can be subdivided according to the neurotransmitter released. The adrenergic nervous system, for which the neurotransmitter is adrenaline (epinephrine) or, more correctly, noradrenaline (norepinephrine), comprises one large subsection. Other, less prominent efferent tracts have γ-aminobutyric acid (GABA), dopamine, or some other substance as the neurotransmitter. The cholinergic nervous system, a second major subdivision, has acetylcholine as the neurotransmitter. Acetylcholine is the neurotransmitter of the neurons to skeletal muscle, of the preganglionic autonomic nerves, and of the postganglionic parasympathetic nerves. Exogenous ACh causes stimulation of the muscles and other structures innervated by these fibers.

This portion of the cholinergic nervous system can be further subdivided into the muscarinic and nicotinic systems, because the structures that are innervated have receptors for the alkaloids muscarine (mAChR) and nicotine (nAChR), respectively, and can be stimulated by these compounds. Mus-

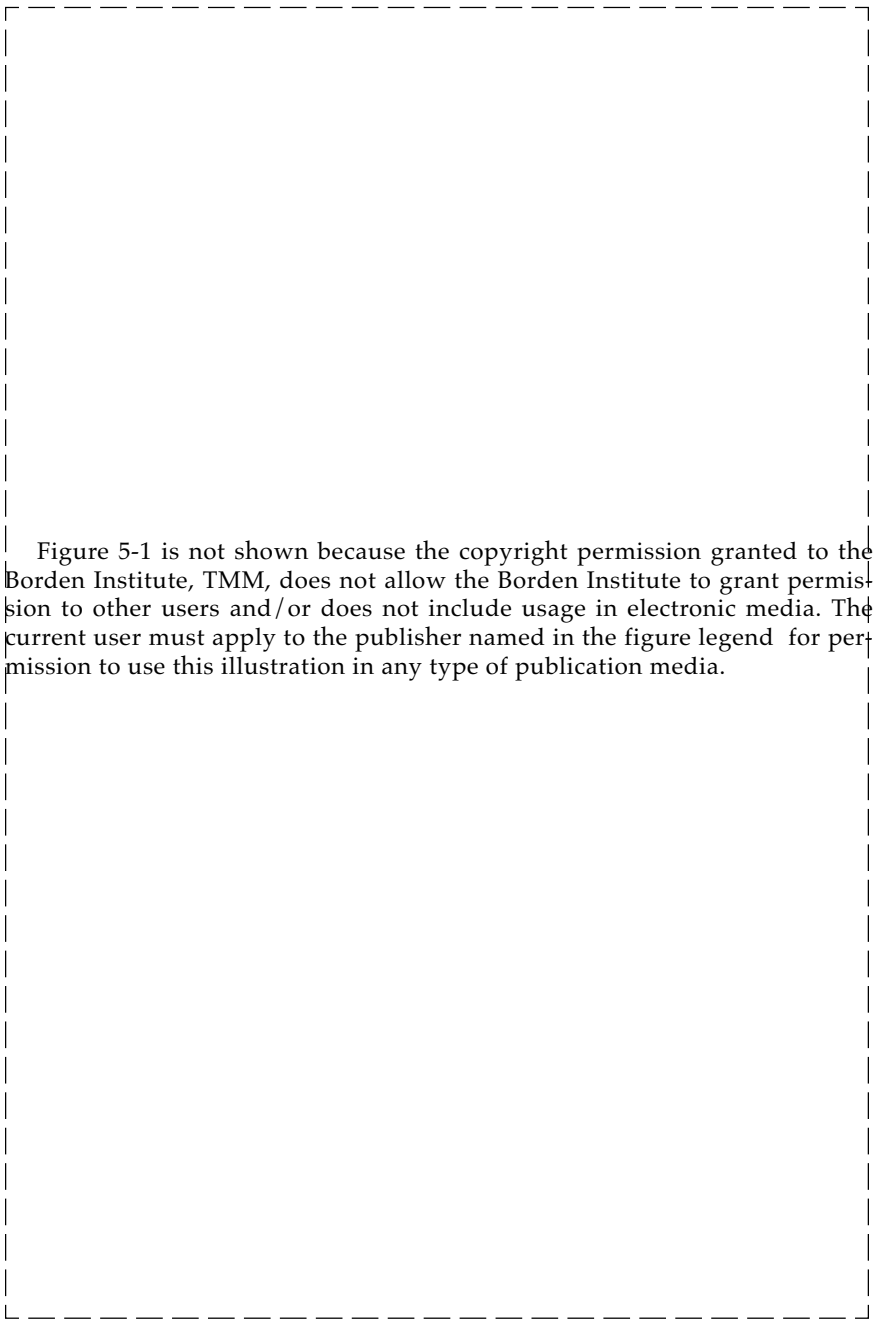

Fig. 5-1. Diagram of neuromuscular conduction. (**a**) Nerve fiber with axon terminal in synaptic trough of muscle. (**b**) Close-up of axon terminal in trough, with synaptic vesicles indicated. (**c**) Acetylcholine synthesis from acetate and choline and storage of acetylcholine in synaptic vesicles. (**d**) Release of acetylcholine from synaptic vesicles after an action potential. (**e**) Acetylcholine stimulation of endplate at receptor for site. (**f**) Hydrolysis of acetylcholine by membrane-bound acetylcholinesterase. Reprinted with permission from *Clinical Symposia*. 1(1,§8): 162, Plate 3118. West Caldwell, NJ: CIBA-GEIGY Medical Education Division.

carinic sites are innervated by postganglionic parasympathetic fibers. These sites include glands (eg, those of the mouth and the respiratory and gastrointestinal systems), the musculature of the pulmonary and gastrointestinal systems, the efferent organs of the cranial nerves (including the heart via the vagus nerve), and other structures. Nicotinic sites are at the autonomic ganglia and skeletal muscles.

The production of a response in an organ to a neuromediated impulse consists of several stages. First, the impulse travels down a nerve to the axonal terminal, or presynaptic area, creating an action potential. (This action potential consists of a change in the resting potential of the polarized nerve membrane.) At the prejunctional area, the action potential stimulates the release of the neurotransmitter ACh from storage in synaptic vesicles. The ACh diffuses across the synaptic cleft and combines with specialized areas—the receptor sites—on the postsynaptic membrane to produce a postsynaptic potential, which may be either a de-

polarization or a hyperpolarization of the membrane. The postsynaptic activity thus initiated is a contractile response in muscle or secretion in a gland. (Events in the central nervous system [CNS] are less clear.) Following each impulse, the neurotransmitter is destroyed to prevent further postsynaptic potentials (Figure 5-1).

In the cholinergic portion of the nervous system, ChE hydrolyzes the neurotransmitter ACh to terminate its activity at the receptor site (Figure 5-2). Acetylcholine attaches to two sites on the ChE enzyme: the choline moiety to the anionic site and the acetyl group to the esteratic site. The choline splits off, leaving the acetylated esteratic site, which then reacts very quickly with water to form acetic acid and regenerated, or reactivated, enzyme.

If AChE were absent from the site, or if it were unable to function, ACh would accumulate and would continue to produce postsynaptic action potentials and activity in the organ. The nerve agents and other ChE-inhibiting substances produce biological activity by disabling (or inhibiting) AChE, an action that leads to an accumulation of ACh. The biological activity, or toxicity, of ChE inhibitors is due to this excess endogenous ACh, which is not hydrolyzed.

Figure 5-2 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Fig. 5-2. This schematic ribbon diagram shows the structure of *Torpedo californica* acetylcholinesterase. The diagram is color-coded; green: the 537-amino acid polypeptide of the enzyme monomer; pink: the 14 aromatic residues that line the deep aromatic gorge leading to the active site; and gold and blue: a model of the natural substrate for acetylcholinesterase, the neurotransmitter acetylcholine, docked in the active site. Reprinted with permission from Sussman JL, Silman I. Acetylcholinesterase: Structure and use as a model for specific cation–protein interactions. *Curr Opin Struct Biol.* 1992;2:724.

The compounds in the two major categories of AChE inhibitors, carbamates and organophosphorus compounds, also attach to the ChE enzyme. There are some differences, however, between them and the natural substrate ACh. Carbamates attach to both the esteratic and the anionic sites. A moiety of the carbamate is immediately split off, leaving the enzyme carbamoylated at the esteratic site. Instead of hydrolysis occurring at this site within microseconds, as it does with the acetylated enzyme, hydrolysis does not occur for minutes to hours, and the enzyme remains inactive or inhibited for about 1 hour after reacting with physostigmine and 4 to 6 hours after reacting with pyridostigmine.

Most organophosphorus compounds combine with the ChE enzyme only at the esteratic site, and the stability of the bond (ie, the interval during which the organophosphorus compound remains attached) depends on the structure of the compound. Hydrolytic cleavage of the compound from the enzyme may occur in several hours if the alkyl groups of the organophosphorus compound are methyl or ethyl, but if the alkyl groups are larger, cleavage may not occur. Thus, the phosphorylated form of the enzyme may remain indefinitely; in this case, return of enzymatic activity occurs only with the synthesis of new enzyme.

Since most of these compounds attach to the esteratic site on AChE, a second binding compound cannot attach on that site if the site is already occupied by a molecule. Thus a previously administered ChE inhibitor will, in a manner of speaking, protect the enzyme from a second one.[14,15] This activity forms the pharmacological basis for administering a carbamate (pyridostigmine) before expected exposure to some nerve agents to provide partial protection (lasting 6–8 h) against the more permanently bound nerve agents. (This mode of protection is described in more detail in Chapter 6, Pretreatment for Nerve Agent Exposure). Because of the different lengths of time required for carbamates and organophosphorus compounds to be hydrolyzed from the enzyme, they are sometimes referred to, respectively, as reversible and irreversible inhibitors.

After inhibition by irreversibly bound inhibitors, recovery of the enzymatic activity in the brain seems to occur more slowly than that in the blood ChE.[16,17] However, one individual severely exposed to sarin was alert and functioning reasonably well for several days while ChE activity in his blood was undetectable (Exhibit 5-1).[18] This case study and other data suggest that tissue function is restored at least partially when ChE activity is still quite low.

EXHIBIT 5-1

CASE REPORT: SARIN EXPOSURE OF A MAN IN FULL PROTECTIVE GEAR

Exhibit 5-1 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Exhibit 5-1 (*continues*)

Exhibit 5-1 (*continued*)

Exhibit 5-1 continued is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Quoted with permission from Sidell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol.* 1974;7(1):6–8.

Blood Cholinesterases

To review, there are two forms of ChE in the blood: BuChE, which is found in plasma or serum, and RBC-ChE, which is associated with erythrocytes. Neither enzyme is identical to the tissue enzyme with the corresponding substrate specificity (butyrylcholine and ACh, respectively). However, because blood can be withdrawn, the activities of each of these enzymes can be assayed by standard, relatively simple laboratory techniques, whereas tissue enzyme is unavailable for assay. The measurements obtained from the blood assay can be used as an approximation of tissue enzyme activity in the event of a known or possible exposure of an animal, such as man, to an AChE inhibitor.

Persons who are occupationally exposed to ChE-inhibiting substances are periodically monitored for asymptomatic exposure by assays of blood-ChE activity. Those at risk include crop sprayers and orchard workers who handle ChE-inhibiting insecticides, and chemical agent–depot workers or laboratory scientists who handle nerve agents. To be meaningful, such monitoring must include knowledge of physiological variation in the blood enzymes.

Individuals who work with or around nerve agents, such as laboratory investigators and depot or storage-yard personnel, have their RBC-ChE activity monitored periodically. Before the individuals begin work, two measures of RBC-ChE, drawn within 14 days but not within 24 hours of each other, are averaged as a "baseline." At periodic intervals, the frequency of which depends on the individuals' jobs, blood is drawn for measuring cholinesterase activity (for further discussion, see Chapter 17, Healthcare and the Chemical Surety Mission). If the activity is 75% or more of their baseline, no action is taken. If the activity is below 75% of their baseline, they are considered to have had an asymptomatic exposure and they are withdrawn from work. Investigations are undertaken to find how they were exposed. Although asymptomatic, they are not permitted to return to a work area around nerve agents until their RBC-ChE activity is higher than 80% of their baseline activity.[19] If an individual has symptoms from a possible nerve agent exposure or if an accident is known to have occurred in his area, his RBC-ChE activity is immediately measured and the criteria noted above, as well as signs and symptoms, are used for exclusion from and re-

turn to work. The values of 75% and 80% were selected for several reasons, including (*a*) the normal variation of RBC-ChE in an individual with time (discussed below), (*b*) laboratory reproducibility in analysis of RBC-ChE activity, and (*c*) the lower tolerance to nerve agents with a low RBC-ChE as demonstrated in animals (discussed below). This topic is also discussed in Chapter 14, Pesticides, in *Occupational Health: The Soldier and the Industrial Base*, another volume in the *Textbook of Military Medicine* series.

Butyrocholinesterase

The enzyme BuChE is present in blood and throughout tissue. Its physiological role in man is unclear[20]; however, it may be important in canine tracheal smooth muscle,[21] the canine ventricular conducting system,[22] and rat atria.[23]

BuChE is synthesized in the liver and has a replacement time of about 50 days. Its activity is decreased in parenchymal liver disease, acute infections, malnutrition, and chronic debilitating diseases, and is increased in the nephrotic syndrome.[20] This enzyme has no known physiological function in blood, but may assist in hydrolyzing certain choline esters.

Persons who have a prolonged paralysis caused by succinylcholine, a muscle relaxant, usually are found to have low BuChE activity.[20] The structure of BuChE is determined by two autosomal alleles. The frequency of occurrence of the gene responsible for abnormal ChE is about 1 in 2,000 to 1 in 4,000 people. Thus, about 96% of the population have the usual phenotype, close to 4% have the heterozygous phenotype, and about 0.03% have the homozygous abnormal phenotype.[20] In addition to having low BuChE activity, which results from this genetic abnormality, in the usual assay, persons with abnormal ChE have low dibucaine numbers (the enzyme activity in an assay in which dibucaine is used as the ChE substrate). The mean dibucaine number for the normal phenotype is about 79%, that for the heterozygote is 62%, and that for the homozygous abnormal phenotype is 16%.[24]

The relationship of BuChE activity and succinylcholine can be somewhat different, however. One author[25] reports on an individual whose BuChE activity was 3-fold higher than normal. His dibucaine number was normal, and he was found to be relatively resistant to succinylcholine. His sister and daughter also had high BuChE activities. The author of this report suggests that this abnormality is autosomal dominant and that it represents another genetic abnormality of BuChE.

Erythrocyte Cholinesterase

RBC-ChE is synthesized with the erythrocyte, which has an average life of 120 days. The activity of this enzyme is decreased in certain diseases involving erythrocytes (such as pernicious anemia) and is increased during periods of active reticulocytosis (such as recovery from pernicious anemia) because reticulocytes have higher ChE activity than do mature cells. No other disease states are known to affect RBC-ChE activity,[20] but one report[26] describes three members of one family who had decreased RBC-ChE activity, suggesting that differences in this enzyme are genetic.

The physiological role of the enzyme in (or on the stroma of) the erythrocyte is unknown. Recovery of RBC-ChE activity after irreversible inhibition takes place only with the synthesis of new erythrocytes, or at a rate of approximately 1% per day.

Variation in Cholinesterase Activities

Butyrocholinesterase. In longitudinal studies[27,28] lasting 3 to 250 weeks, the coefficient of variation (standard deviation divided by the mean) for an individual's BuChE activity ranged from 5% to 11.8% in men and women. Of the ranges (range is defined as the difference between the highest and lowest activities divided by the mean) for individuals in the study, the lowest was 24% and the highest was 50% over 1 year.[28]

BuChE activity does not vary with age in women[29,30] until the age of 60 years, when higher BuChE activities are seen.[30] BuChE activities in men have been reported in some studies to increase with age and in other studies to decrease with age.[20] In matched age groups, BuChE activity was higher in men than in women,[20,30] and higher in women not taking oral contraceptives than in those taking them.[30–32]

Erythrocyte Cholinesterase. RBC-ChE activity is more stable than the activity of the BuChE.[28,33,34] In a study[28] that lasted 1 year, the coefficients of variation were 2.1% to 3.5% in men and 3.1% to 4.1% in women, with ranges of 7.9% to 11.4% in men and 12.0% to 15.9% in women. This variation was less than that observed for the hematocrits of these individuals.

It is unclear whether age affects RBC-ChE activity. In one study,[29] RBC-ChE activity was unchanged with age, while in another,[30] enzyme activity increased with age from the third to the sixth decades in men, with a less marked increase through the fifth decade in women.

Inhibition of Blood Cholinesterases

Some ChE-inhibiting substances inhibit BuChE preferentially, and some inhibit RBC-ChE preferentially. Large amounts of ChE inhibitors will completely inhibit both enzymes.

The blood enzymes appear to act as buffers for the enzymes in the tissue. There is little inhibition of tissue enzyme until much of the blood enzyme is inhibited. The RBC-ChE appears to be more important than the plasma enzyme in this regard. In two studies,[35,36] a small dose of DFP in humans inhibited about 90% of the plasma enzyme activity but only 15% to 20% of RBC-ChE activity. Symptoms correlated with depression of RBC-ChE, but not with depression of BuChE (see the Central Nervous System and Behavior section below). In humans, some pesticides, such as parathion,[37–39] systox,[37] and malathion,[20] also preferentially inhibit the plasma enzyme, while others, such as dimefox[39] and mevinphos,[40] initially bind with the RBC enzyme. In animals, there appears to be a species difference, inasmuch as parathion preferentially inhibits RBC-ChE in rats and the plasma enzyme in dogs.[20]

The nerve agent VX preferentially inhibits RBC-ChE; in two studies,[41,42] a small amount caused a 70% or greater decrease in the activity of this enzyme, whereas the activity of BuChE was inhibited by no more than 20%. Sarin also preferentially inhibits the RBC-ChE; 80% to 100% inhibition of RBC-ChE activity was observed in two studies,[35,43] while BuChE was inhibited by 30% to 50%. Therefore, estimation of the RBC-ChE activity provides a better indicator of acute nerve agent exposure than does estimation of the plasma enzyme activity.

When the blood enzymes have been irreversibly inhibited, recovery of ChE activity depends on production of new plasma enzymes or production of new erythrocytes. Hence, complete recovery of BuChE activity that has been totally inhibited by sarin will occur in about 50 days, and recovery of the RBC-ChE, in 120 days (about 1% per day).[44] In humans, after inhibition by VX, the RBC-ChE activity seems to recover spontaneously at the rate of about 0.5% to 1% per hour for a few days, but complete recovery depends on erythrocyte production.[41,42]

Time Course of Inhibition. After very large amounts of nerve agent (multiple LD_{50}s [ie, multiples of the dose that is lethal to 50% of the exposed population]) are placed on the skin, signs and symptoms occur within minutes, and inhibition of blood ChE activities occurs equally quickly. However, with smaller amounts of agent, the onset is not so rapid. In studies in which small amounts of VX were applied on the skin of humans, the onset of symptoms and the maximal inhibition of blood ChE activity were found to occur many hours after application of the agent. In one study[42] in which equipotent amounts of VX were applied to the skin in different regions, the time to maximal inhibition was 5 hours for the head and neck, 7 hours for the extremities, and 10 hours for the torso. In a similar study,[45] the average time from placing VX on the skin to the onset of nausea and vomiting and maximal drop of blood ChE activity was 10.8 hours.

In a third study,[46] VX was applied to the cheek or forearm at environmental temperatures ranging from 0°F to 124°F, and 3 hours later the subjects were decontaminated and taken to a recovery area (about 80°F). In all temperature groups, the RBC-ChE activity continued to decline after decontamination, and maximal inhibition occurred at 5.6 hours after exposure at 124°F, 8.5 hours after exposure at 68°F, 10.4 hours after exposure at 36°F, and 12.2 hours after exposure at 0°F. At the two lowest temperatures, the rates of agent penetration and of decline in RBC-ChE activity increased after the subjects were taken from the cold environment and decon-

TABLE 5-1

RELATION OF EFFECTS OF NERVE AGENT EXPOSURE TO ERYTHROCYTE CHOLINESTERASE ACTIVITY

Table 5-1 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Adapted with permission from Sidell FR. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents.* New York, NY: Academic Press; 1992: 163.

taminated. These results suggest that agent absorption through the skin is more rapid and complete at higher temperatures, and that even after thorough decontamination, a considerable amount of agent remains in the skin to be absorbed.

Inhalation of nerve agent vapor inhibits blood ChE activity and produces signs and symptoms of exposure more rapidly than does dermal contact. Although there is no correlation between ChE activity and clinical effects after exposure to small amounts of vapor, both clinical effects and ChE inhibition occur within minutes. In one study,[41] both the maximal inhibition of RBC-ChE activity and the appearance of signs and symptoms occurred about 1 hour after intravenous administration of small amounts of VX. After ingestion of VX, the interval was 2 to 3 hours.

Relation to Signs and Symptoms. The local signs and symptoms in the eye, nose, and airways caused by small amounts of vapor are due to the direct effect of the vapor on the organ; no correlation between the severity of these effects and the blood ChE activity seems to exist. These early experimental data[47–49] indicating the lack of correlation were supported by a retrospective analysis of 62 individuals seen at the Edgewood Arsenal Toxic Exposure Aid Station between 1948 and 1972. Although all individuals had physical signs or definite symptoms (or both) of nerve agent vapor exposure, there was no correlation between local effects from vapor exposure and RBC-ChE activity (Table 5-1).[50]

Minimal systemic effects, such as vomiting, occur in half the population when the RBC-ChE is inhibited to 25% of its control activity.[41,42] In a study[42] in which VX was placed on the skin, no vomiting occurred in 30 subjects whose minimal RBC-ChE activities were 40% of control or higher. Vomiting occurred in 9 (43%) of 21 subjects whose minimal RBC-ChE activities were 30% to 39% of control, in 10 (71%) of 14 subjects whose minimal enzyme activities were 20% to 29% of control, and in 3 (60%) of 5 subjects whose minimal RBC-ChE activities were 0% to 19% of control. In other instances, patients had an RBC-ChE activity of 0% without the expected symptoms; this inhibition was acutely induced (personal observation).

Table 5-2 categorizes data from 283 individuals (data are from published sources[41,42] and unpublished research) who received VX by various routes; the numbers of subjects, the activity ranges of RBC-ChE, and the numbers and percentages of those who vomited are shown. The degree of inhibition needed to cause vomiting in these 283 people corresponds to that found in experimental data from other sources, which indicate that "to exert significant actions in vivo, an anti-ChE must inhibit from 50% to 90% of the enzyme present."[11(p446)]

TABLE 5-2

RELATION OF CHOLINESTERASE ACTIVITY TO VOMITING AFTER EXPOSURE TO VX

Table 5-2 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Adapted with permission from Sidell FR. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. New York, NY: Academic Press; 1992: 163.

Nerve Agents

Molecular models of the nerve agents tabun, sarin, soman, and VX are shown in Figure 5-3. Table 5-3 summarizes the chemical, physical, environmental and biological properties of these compounds.

Nerve agents differ from commonly used ChE inhibitors primarily because they are more toxic (ie, a smaller amount is needed to cause an effect on an organism). For example, an in vitro study[43] with ChE from human erythrocytes, brain, and muscle showed that sarin had about 10-fold more inhibitory activity than TEPP, 30-fold more than neostigmine, 100-fold more than DFP, and 1,000-fold more than parathion.

The vapor or aerosol exposure (the product of concentration [C] and time [t]) needed to cause

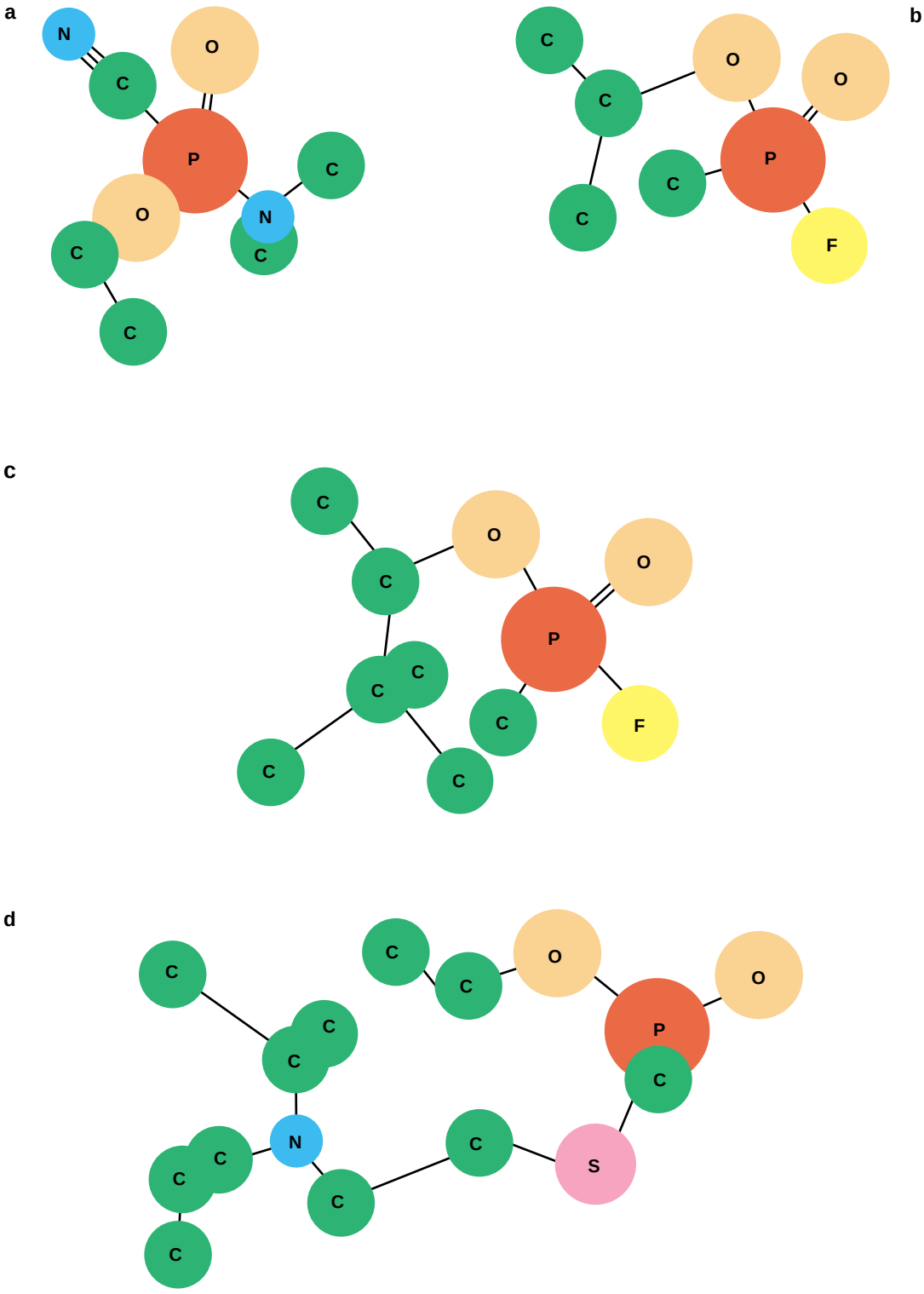

Fig. 5-3. Molecular models of (**a**) tabun (GA), (**b**) sarin (GB), (**c**) soman (GD), and (**d**) VX. Molecular models: Courtesy of Offie E. Clark, US Army Medical Research Institute of Chemical Defense, Aberdeen, Md.

TABLE 5-3

CHEMICAL, PHYSICAL, ENVIRONMENTAL, AND BIOLOGICAL PROPERTIES OF NERVE AGENTS

Properties	Tabun (GA)	Sarin (GB)	Soman (GD)	VX
Chemical and Physical				
Boiling Point	230°C	158°C	198°C	298°C
Vapor Pressure	0.037 mm Hg at 20°C	2.1 mm Hg at 20°C	0.40 mm Hg at 25°C	0.0007 mm Hg at 20°C
Density:				
Vapor (compared to air)	5.6	4.86	6.3	9.2
Liquid	1.08 g/mL at 25°C	1.10 g/mL at 20°C	1.02 g/mL at 25°C	1.008 g/mL at 20°C
Volatility	610 mg/m^3 at 25°C	22,000 mg/m^3 at 25°C	3,900 mg/m^3 at 25°C	10.5 mg/m^3 at 25°C
Appearance	Colorless to brown liquid	Colorless liquid	Colorless liquid	Colorless to straw-colored liquid
Odor	Fairly fruity	No odor	Fruity; oil of camphor	Odorless
Solubility:				
In Water	9.8 g/100 g at 25°C	Miscible	2.1 g/100 g at 20°C	Miscible < 9.4°C
In Other Solvents	Soluble in most organic solvents	Soluble in all solvents	Soluble in some solvents	Soluble in all solvents
Environmental and Biological				
Detectability:				
Vapor	M8A1, M256A1, CAM, ICAD	M8A1, M256A1, CAM, ICAD	M8A1, M256A1, CAM, ICAD	M8A1, M256A1, CAM, ICAD
Liquid	M8, M9 paper	M8, M9 paper	M8, M9 paper	M8, M9 paper
Persistency:				
In Soil	Half-life 1–1.5 d	2–24 h at 5°C–25°C	Relatively persistent	2–6 d
On Materiel	Unknown	Unknown	Unknown	Persistent
Decontamination of Skin	M258A1, diluted hypochlorite, soap and water, M291 kit	M258A1, diluted hypochlorite, soap and water, M291 kit	M258A1, diluted hypochlorite, soap and water, M291 kit	M258A1, diluted hypochlorite, soap and water, M291 kit
Biologically Effective Amount:				
Vapor	LCt_{50}: 400 mg•min/m^3	LCt_{50}: 100 mg•min/m^3	LCt_{50}: 50 mg•min/m^3	LCt_{50}: 10 mg•min/m^3
Liquid	LD_{50} (skin): 1.0 g/70-kg man	LD_{50} (skin): 1.7 g/70-kg man	LD_{50} (skin): 350 mg/70-kg man	LD_{50} (skin): 10 mg/70-kg man

CAM: chemical agent monitor; ICAD: individual chemical agent detector; LCt_{50}: vapor or aerosol exposure necessary to cause death in 50% of the population exposed; LD_{50}: dose necessary to cause death in 50% of the population with skin exposure; M8A1: chemical alarm system; M256A1: detection card; M258A1: self-decontamination kit; M291: decontamination kit; M8 and M9: chemical detection papers

death in 50% of the exposed population is known as the LCt_{50} (Exhibit 5-2); the estimated LCt_{50}s for humans for these four agents are as follows:

- for tabun vapor, 400 mg•min/m^3,
- for sarin vapor, 100 mg•min/m^3,
- for soman vapor, 50 mg•min/m^3, and
- for VX vapor, 10 mg•min/m^3.

In comparison, the estimated LCt_{50} for hydrogen cyanide is 2,500 to 5,000 mg•min/m^3.

The estimated percutaneous LD_{50}s for the four compounds are as follows:

- for tabun, 1,000 mg,
- for sarin, 1,700 mg,
- for soman, 350 mg, and

EXHIBIT 5-2

DEFINITIONS OF C*t*, LCt_{50}, AND LD_{50}

For comparative purposes, the terms C*t* and LCt_{50} are often used to express the dose of a vapor or aerosol. However, the terms do not describe inhaled doses; they actually describe the amount of compound to which an organism is *exposed*.

- The term C*t* is used to describe an estimate of dose. C represents the concentration of the substance (as vapor or aerosol) in air (usually expressed as mg/m^3) and *t* represents time (usually expressed in minutes).
- The C*t* value is the product of the concentration (C) to which an organism is exposed multiplied by the time (*t*) during which it remains exposed to that concentration. C*t* does not express the amount retained within an organism; thus, it is not an inhalational dose.
- Since C*t* is a product of C • *t*, a particular value can be produced by inversely varying the values of C and *t*. The C*t* to produce a given biological effect is usually constant over an interval of minutes to several hours (Haber's Law). Thus, an effect that is produced by an exposure to 0.05 mg/m^3 for 100 minutes is also produced by an exposure to 5 mg/m^3 for 1 minute (C*t* = 5 mg•min/m^3 in both cases). This generalization usually is not valid for very short or very long times, however. The organism may hold its breath for several seconds and not actually inhale the vapor; over many hours, some detoxification may occur in the organism.
- The term LCt_{50} is often used to denote the vapor or aerosol exposure (C*t*) necessary to cause death in 50% of the population exposed (L denotes lethal, and 50 denotes 50% of the population). In the same manner, the term LD_{50} is used to denote the dose that is lethal for 50% of the population exposed by other routes of administration.

- for VX, 6 to 10 mg.

VX has a much lower LD_{50} because it is much less volatile and remains intact on the skin, whereas the other nerve agents will evaporate unless covered (eg, by clothing).[6,8] Different sources provide different estimates for these LD_{50} and LCt_{50} values; however, those noted above seem to be the most commonly accepted.

The four nerve agents are liquid at moderate temperatures; thus, the term "nerve gas" is a misnomer. In their pure state, they are clear, colorless, and, at least in dilute solutions of distilled water, tasteless. Tabun has been reported to have a faint, slightly fruity odor, and soman, to have an ill-defined odor; sarin and VX are apparently odorless.

The G agents are volatile; VX has very low volatility. Sarin, the most volatile, is somewhat less volatile than water; tabun and soman are less volatile than sarin. The G agents present a definite vapor hazard; VX is much less likely to unless the ambient temperature is high.

EXPOSURE ROUTES

Inhalational Exposure to Vapor

The effects produced by nerve agent vapor begin in seconds to minutes after the onset of exposure, depending on the concentration of vapor. These effects usually reach maximal severity within minutes after the individual is removed from or protected from the vapor or may continue to worsen if the exposure continues. There is no delay in onset as there is after liquid exposure.

At low C*t*s, the eyes, nose, airways, or a combination of these organs are usually affected. The eyes and nose are the most sensitive organs; the eyes may be affected equally or unequally. There may be some degree of miosis (with or without associated conjunctival injection and pain) with or without rhinorrhea, or there may be rhinorrhea without eye involvement (Table 5-4).

As exposure increases slightly, the triad of eye, nose, and lung involvement is usually seen. The casualty may or may not notice dim vision and may complain of "tightness in the chest." "Tightness in the chest" may occur in the absence of physical findings. At higher exposures, the effects in these organs intensify. Marked miosis, copious secretions from the nose and mouth, and signs of moderate-to-severe impairment of ventilation are seen. The casualty will complain of mild-to-severe dyspnea,

TABLE 5-4

EFFECTS OF EXPOSURE TO NERVE AGENT VAPOR

Table 5-4 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Adapted with permission from Sidell FR. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. New York, NY: Academic Press; 1992: 173.

may be gasping for air, and will have obvious secretions.

In severe exposures, the casualty may not have time to report the initial effects before losing consciousness, and may not remember them on awakening. One severely exposed individual later recalled that he noticed an increase in secretions and difficulty in breathing, and another said he felt giddy and faint before losing consciousness. In both instances, the casualties were unconscious within

TABLE 5-5

EFFECTS OF DERMAL EXPOSURE TO LIQUID NERVE AGENTS

Table 5-5 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Adapted with permission from Sidell FR. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. New York, NY: Academic Press; 1992: 175.

less than a minute after exposure to agent vapor. When reached (within minutes) by rescuers, both were unconscious and exhibited convulsive jerking motions of the limbs; copious secretions from the mouth and nose; very labored, irregular, and gasping breathing; generalized muscular fasciculations; and miosis. One developed flaccid paralysis and apnea a minute or two later. The other received immediate, vigorous treatment, and his condition did not progress (personal observation).

Dermal Exposure to Liquid

The early effects of a drop of nerve agent on the skin and the time of onset of these effects depend on the amount of nerve agent and several other factors, such as the site on the body, the temperature, and the humidity. After a delay during which the individual is asymptomatic, localized sweating occurs at the site of the droplet; less commonly, there are localized fasciculations of the underlying muscle (Table 5-5). Unless the amount of the nerve agent is in the lethal range, the next effects (or perhaps the first effects, if the sweating and fasciculations do not occur or are not noticed) are gastrointestinal: nausea, vomiting, diarrhea, or a combination of these symptoms. The casualty may notice generalized sweating and complain of tiredness or otherwise feeling ill. There may be a period of many hours between exposure and the appearance of symptoms and signs. These signs and symptoms might occur even if the casualty has been decontaminated.[46]

After large exposures, the time to onset of effects may be much shorter than for smaller exposures and decreases as the amount of agent increases. For instance, two individuals were decontaminated within minutes of exposure to a drop of nerve agent. There was a 15- to 20-minute, asymptomatic interval before the precipitant onset of effects: collapse, loss of consciousness, convulsive muscular jerks, fasciculations, respiratory embarrassment, and copious secretions. Within several minutes, flaccid paralysis and apnea occurred in both (personal observation).

EFFECTS ON ORGANS AND ORGAN SYSTEMS

Most of the information on the effects of nerve agents on organ systems in humans is derived from studies done in the post–World War II period, from reports of people exposed to pesticides, or from clinical evaluations of accidental exposures of people who worked in nerve agent–research laboratories, manufacturing facilities, or storage areas or depots (Table 5-6). Some organ systems have been studied more intensively than others; for some organ systems there are few human data. For example, for the musculoskeletal system, there is a plethora of data from animal studies and studies in isolated neuromuscular preparations, but study results are difficult to apply to a human clinical situation.

The Eye

Nerve agents in the eye may cause miosis, conjunctival injection, pain in or around the eye, and dim or blurred vision (or both). Reflex nausea and vomiting may accompany eye exposure. These effects are usually local, occurring when the eye is in direct contact with nerve agent vapor, aerosol, or liquid, but exposure by other routes (such as on the skin) can also affect the eyes. Because eyes often react late in the course of intoxication in the latter case (exposure on the skin), they cannot be relied on as an early indication of exposure.

Systemic (such as skin or peroral) exposure to a nerve agent might be large enough to produce moderate symptoms (nausea, vomiting) without miosis. In studies[41,42,45] in which VX was placed on the skin, administered intravenously, or given orally, a significant number of subjects experienced nausea, vomiting, sweating, or weakness, but none had miosis. In 47 patients with parathion poisoning, all of the 14 severe cases had miosis, whereas 6 of 11 patients with moderate poisoning and only 5 of 22 patients with mild effects had miosis.[51] On the other hand, a vapor or aerosol exposure might cause miosis without other signs or symptoms and an exposure in one eye will cause miosis in that eye (a local effect because of a mask leak in one eyepiece or similar causes) without affecting the other eye.

If the eye exposure is not associated with inhalation of the nerve agent, there is no good correlation between severity of the miosis and inhibition of RBC-ChE activity. The latter may be relatively normal or may be inhibited by as much as 100% (see Table 5-1), so the severity of the miosis cannot be used as an index of the amount of systemic absorption of agent or amount of exposure. On the other hand, an early study[52] demonstrated a relationship between the Ct of sarin and pupil size at the time of maximal miosis, and the investigator suggested that the pupil size might be used as an index of the amount of exposure.

Unilateral miosis is sometimes seen in workers handling nerve agents or insecticides and usually occurs because of a small leak in the eyepiece of

TABLE 5-6

EFFECTS OF NERVE AGENTS IN HUMANS

Table 5-6 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Adapted with permission from Sidell FR. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. New York: Academic Press; 1992: 162.

the protective mask. Again, the RBC-ChE may or may not be inhibited (see Table 5-1). The unilateral miosis has no prognostic medical significance. However, there may be problems with judging distances (that is, depth perception). This impairment may cause difficulty in activities such as driving a car or piloting an airplane, which require stereovisual coordination (the Pulfrich stereo effect).[20]

The onset of miosis may be within seconds to minutes of the start of exposure; if the concentration of agent vapor or aerosol is quite low, maximal miosis may not occur until an hour or longer following exposure. The duration varies according to the amount of agent. The pupils may regain their ability to react to normal levels of indoor lighting within several days after exposure, but their ability to dilate maximally in total darkness may not return for as long as 9 weeks (Figure 5-4 and Exhibit 5-3).[18,53]

The effects of nerve agents on vision have been studied for decades. Characteristically, an unprotected individual exposed to nerve agent will have the signs discussed above and may complain of dim vision, blurred vision, or both.

Light Reduction

Dim vision is generally believed to be related to the decrease in the amount of light reaching the retina because of miosis. In a study[54] in which miosis was induced in one eye by instillation of sarin, the decrease in visual sensitivity correlated with the reduction in the area of pupillary aperture. Fifty-three subjects accidentally exposed to G agents reported improvements in dim vision before the miosis improved, which suggests that factors other than a small pupil are responsible for the high light threshold.[55] In another study,[56] however, no change in visual threshold was measured after miosis was induced by instillation of sarin onto the eye; the light threshold increased after systemic administration of sarin vapor with the eyes protected, so that no miosis occurred. The threshold was reduced to normal following systemic administration of atropine sulfate (which enters the CNS), but not after administration of atropine methylnitrate (which does not enter the CNS).[57] The authors suggested that the dimness of vision was due

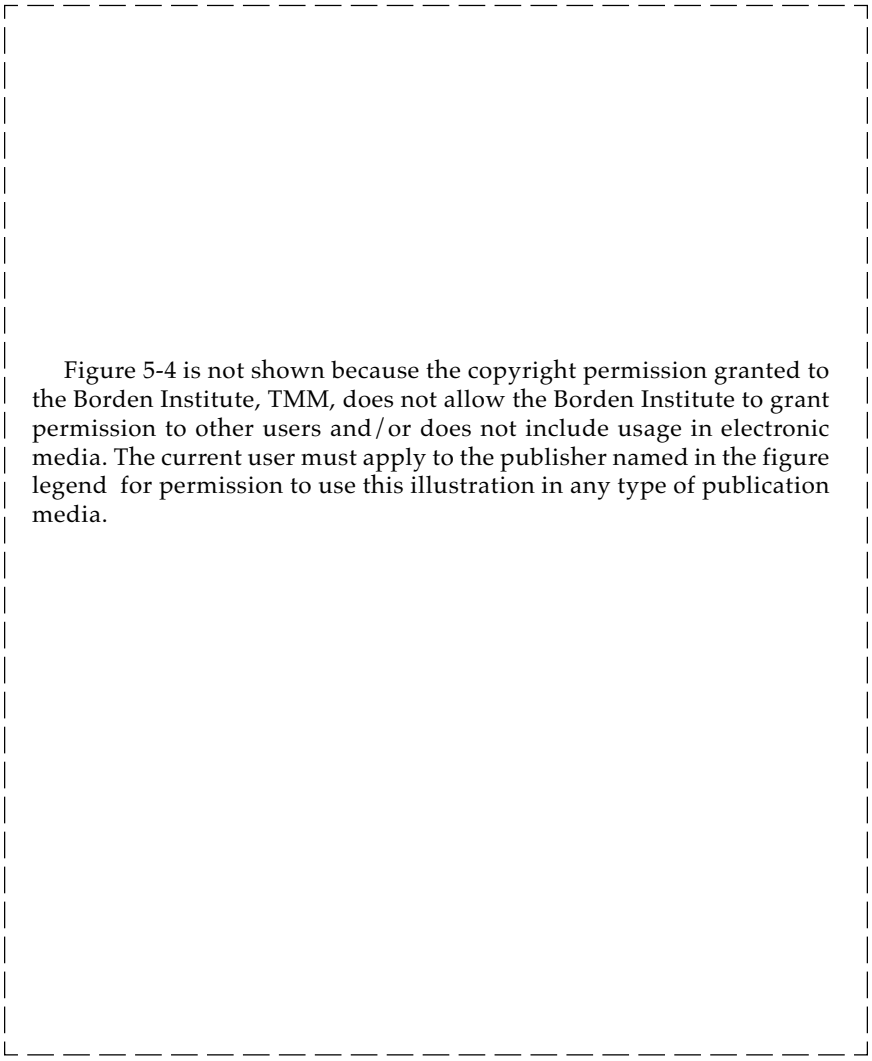

Fig. 5-4. This man was accidentally exposed to an unknown amount of nerve agent vapor. The series of photographs shows his eyes gradually recovering their ability to dilate. All photographs were taken with an electronic flash (which is too fast for the pupil to react) after the subject had been sitting in a totally dark room for 2 minutes. These photographs were taken (from top to bottom) at 3, 6, 13, 20, 41, and 62 days after the exposure. Subsequent photographs indicate that the eyes did not respond fully to darkness for 9 weeks; maximal dilation was reached on day 62 after the exposure. Reprinted with permission from Sidell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol.* 1974;7:11.

to neural mechanisms in the retina or elsewhere in the CNS.

Although the dim vision reported by persons exposed to nerve agent vapor is generally ascribed to miosis, the above accounts suggest that more-central neural mechanisms may have equal or greater importance. In the case of the carbamate physostigmine, an increase in light sensitivity (a decreased threshold) after intramuscular administration of the drug has been reported.[58] However, carbamates may differ from nerve agents in their effects on vision.

Regardless of its cause, reduction in visual sensitivity impairs those who depend on vision in dim light: individuals who watch a tracking screen, monitor visual displays from a computer, or drive a tank in the evening or at night. As a practical matter, anyone whose vision has been affected by exposure to a nerve agent should not be allowed to drive in dim light or in darkness.

Visual Acuity

Persons exposed to nerve agents sometimes complain of blurred as well as dim vision. In one study,[59] visual acuity was examined in six subjects before and after exposure to sarin vapor at a Ct of 15 mg•min/m^3. Near visual acuity was not changed in any of the six after exposure and was worsened after an anticholinergic drug (cyclopentolate) was instilled in the eyes. Far visual acuity was unchanged after sarin exposure in five of the six subjects and was improved in the sixth, who nonetheless complained that distant vision was blurred after sarin.

Two presbyopic workers who were accidentally exposed to sarin had improved visual acuity for days

EXHIBIT 5-3

CASE REPORT: EXPOSURE OF THREE MEN TO SARIN

Exhibit 5-3 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Quoted with permission from Sidell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol*. 1974;7(1):9.

after exposure. As the effects of the agent decreased, their vision returned to its previous state; in each case, this took about 35 days.[53] The author suggested, as others have previously, that miosis accounted for the improvement in visual acuity (the pinhole effect).

Eye Pain

Eye pain may accompany miosis, but the reported incidence varies. A sharp pain in the eyeball or an aching pain in or around the eyeball is common. A mild or even severe headache (unilateral if the miosis is unilateral) may occur in the frontal area or throughout the head. This pain is probably caused by ciliary spasm and is worsened by looking at bright light, such as the light from a match a person uses to light a cigarette (the "match test"). Sometimes this discomfort is accompanied by nausea, vomiting, and malaise.

Local instillation of an anticholinergic drug such as atropine or homatropine usually brings relief from the pain and systemic effects (including the nausea and vomiting), but because these drugs cause blurring of vision, they should not be used unless the pain is severe.[59]

The Nose

Rhinorrhea is common after both local and systemic nerve agent exposure. It may occur soon after exposure to a small amount of vapor and sometimes precedes miosis and dim vision, or it may occur in the absence of miosis. Even a relatively small exposure to vapor may cause severe rhinorrhea. One exposed worker compared the nasal secretions to the flow from a leaking faucet, and another said that they were much worse than those produced by a cold or hay fever (personal observation).

Rhinorrhea also occurs as part of an overall, marked increase in secretions from glands (salivary, pulmonary, and gastrointestinal) that follows a severe systemic exposure from liquid on the skin and, under this circumstance, becomes a secondary concern to both the casualty and the medical care provider.

Pulmonary System

After exposure to a small amount of nerve agent vapor, individuals often complain of a tight chest

(difficulty in breathing), which is generally attributed to spasm or constriction of the bronchiolar musculature. Secretions from the goblet and other secretory cells of the bronchi also contribute to the dyspnea. Exposure to sarin at a C*t* of 5 to 10 mg•min/m^3 will produce some respiratory discomfort in most individuals, with the discomfort and severity increasing as the amount of agent increases.

Several decades ago, investigators attempted to characterize pulmonary impairment caused by exposure to nerve agents by performing pulmonary function studies (such as measurements of vital capacity and maximal breathing capacity) on subjects exposed to small amounts of sarin vapor (the C*t* values for sarin ranged up to 19.6 mg•min/m^3).[60] Some observers found increases in airway resistance[61] and other changes, while other researchers did not.[62]

Although these studies yielded conflicting results, clinical practitioners have found that the inhalation of nerve agent vapor or aerosol causes dyspnea and pulmonary changes that usually are audible on auscultation. These changes are noticeable after low C*t* exposures (5–10 mg•min/m^3) and intensify as the C*t* increases. The pulmonary effects begin within seconds after inhalation. If the amount inhaled is large, the effects of the agent include severe dyspnea and observable signs of difficulty with air exchange, including cyanosis.

If the amount of the inhaled agent is small, a casualty may begin to feel better within minutes after moving into an uncontaminated atmosphere, and may feel normal in 15 to 30 minutes. It was not uncommon, for example, for individuals who had not received atropine or other assistance to arrive at the Edgewood Arsenal Toxic Exposure Aid Station about 15 to 20 minutes after exposure and report that their initial, severe trouble in breathing had already decreased markedly (personal observation). If the exposure was larger, however, relief was likely to come only after therapeutic intervention, such as administration of atropine.

Attempts to aid ventilation in severely poisoned casualties can be greatly impeded by constriction of the bronchiolar musculature and by secretions. One report[63] mentions thick mucoid plugs that hampered attempts at assisted ventilation until the plugs were removed by suction. Atropine may contribute to the formation of this thicker mucus because it dries out the thinner secretions.

A severely poisoned casualty becomes totally apneic and will die as a result of ventilatory failure, which precedes collapse of the circulatory system. Many factors contribute to respiratory failure, including obstruction of air passages by bronchoconstriction and secretions; weakness followed by flaccid paralysis of the intercostal and diaphragmatic musculature, which is needed for ventilation; and a partial or total cessation of stimulation to the muscles of respiration from the CNS, indicating a defect in central respiratory drive.

Older data on the relative contributions of each of these factors in causing death were summarized in a report[64] describing original studies in nine species. The authors concluded that central respiratory failure appeared to dominate in most species, but its overall importance varied with the species, the agent, and the amount of agent. For example, under the circumstances of the studies, failure of the central respiratory drive appeared to be the major factor in respiratory failure in the monkey, whereas bronchoconstriction appeared early and was severe in the cat. The authors of another report[65] suggest that the presence of anesthesia, which is used in studies of nerve agent intoxication in animals, and its type and depth are also factors in establishing the relative importance of central and peripheral mechanisms.

In another study,[66] bronchoconstriction seen in the dog after intravenous sarin administration was quite severe compared with that found in the monkey (however, the dog is known to have thick airway musculature). Differences in circulatory and respiratory effects were seen between anesthetized and unanesthetized dogs given sarin.[67] Convulsions and their associated damage were not seen in the anesthetized animals. In this study, there were no significant differences in the cardiovascular and respiratory effects when the agent was given intravenously, percutaneously, or by inhalation. In a study[68] of rabbits poisoned with sarin, bronchoconstriction appeared to be a minor factor, while neuromuscular block (particularly at the diaphragm) and central failure were the primary factors in respiratory failure.

In a recent review[69] describing studies in anesthetized cats given tabun, sarin, soman, or VX, the loss of central respiratory drive was found to be the predominant cause of respiratory failure with each of the agents, and the contribution of bronchoconstriction was apparently insignificant (in contrast to the severe bronchoconstriction noted in the earlier study[64]). Thus, respiratory failure was the predominant cause of death in the species studied inasmuch as significant cardiovascular depression occurred only after cessation of respiration.[68,69]

When atropine was administered in adequate amounts before the failure of circulation, it reversed the central depression and bronchoconstriction but not the neuromuscular block, a finding that might be expected, because the neuromuscular effects of poisoning with these nerve agents occur at a nicotinic site.[64,68]

In a recent study,[70] pyridostigmine, a drug currently fielded as a pretreatment, was administered to primates, which then were exposed to a nerve agent and given the standard therapeutic drugs, atropine and 2-pyridine aldoxime methyl chloride (2-PAM Cl, also called 2-pralidoxime chloride; pyridine-2-aldoxime methyl chloride; 2-formyl-1-methylpyridinium chloride; Protopam chloride, manufactured by Wyeth-Ayerst Laboratories, Philadelphia, Pa; see section below on oximes). Pyridostigmine does not appear to enter the CNS because it is a quaternary compound and thus would not be expected to protect central sites of respiratory stimulation against the effects of a nerve agent. The pretreated animals continued to breathe, however, in contrast to controls that did not receive pyridostigmine pretreatment but were otherwise treated in the same manner.

The results of this study suggest that pyridostigmine protects against the cessation of respiration. Since pyridostigmine appears not to enter the CNS, this suggests that peripheral mechanisms of breathing (skeletal muscles and airways) must predominate in sustaining breathing. Alternatively, the blood–brain barrier may change in the presence of a nerve agent (as with other types of poisoning or hypoxia) to allow the penetration of drugs it otherwise excludes. For example, when 2-PAM Cl, which is also a quaternary compound, is administered to animals poisoned with a ChE inhibitor, it can be found in their CNS, but it is not found in the brains of normal animals after they receive 2-PAM Cl.[71]

Skeletal Musculature

The neuromuscular effects of nerve agents have been the subject of hundreds of studies since nerve agents were first synthesized in 1936. Much of our information on the mechanism of action of nerve agents and potential therapeutic measures has come from these studies. Because this chapter is primarily concerned with clinical effects of nerve agent poisoning, a comprehensive review of these studies is not presented here.

The effects of nerve agent intoxication on skeletal muscle are caused initially by stimulation of muscle fibers, then by stimulation of muscles and muscle groups, and later by fatigue and paralysis of these units. These effects on muscle may be described as fasciculations, twitches (or jerks), and fatigue.

Fasciculations are the visible contractions of a small number of fibers innervated by a single motor nerve filament. They appear as ripples under the skin. They can occur as a local effect at the site of a droplet of agent on the skin before enough agent is absorbed to cause systemic effects. They also can appear simultaneously in many muscle groups after a large systemic exposure. A casualty who has sustained a severe exposure will have generalized fasciculations, a characteristic sign of poisoning by a ChE inhibitor; typically, fasciculations will continue long after the patient has regained consciousness and has voluntary muscle activity.

After a severe exposure, there are intense and sudden contractions of large muscle groups, which cause the limbs to flail about or momentarily become rigid or the torso to arch rigidly in hyperextension. Whether these movements, which have been described as convulsive jerks, are part of a generalized seizure or originate lower in the nervous system is unclear. Occasionally, these disturbances may be a local effect on the muscle groups below or near the site of exposure—for instance, the marked trismus and nuchal rigidity in an individual who pipetted soman into his mouth (Exhibit 5-4).[18] After several minutes of hyperactivity (fasciculations or twitching), the muscles fatigue and flaccid paralysis occurs. This, of course, stops convulsive activity and respiration.

Central Nervous System and Behavior

Behavioral and psychological changes in humans exposed to ChE-inhibiting substances have been discussed in numerous reports. The incidence of psychological effects is higher in individuals who have had more severe exposures to nerve agents, but they may occur—probably more frequently than is commonly recognized—in individuals who have received a small exposure and have no or minimal physical signs or symptoms. Although the effects may begin as late as 1 day after exposure, they usually start within a few hours and last from several days to several weeks. Common complaints include feelings of uneasiness, tenseness, and fatigue. Exposed individuals may be forgetful, and observers may note that they are irritable, do not answer simple questions as quickly and precisely as usual, and generally display impaired judgment, poor

EXHIBIT 5-4

CASE REPORT: ACCIDENTAL EXPOSURE OF A MAN TO LIQUID SOMAN

Exhibit 5-4 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Exhibit 5-4 (*continued*)

Exhibit 5-4 continued is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Quoted with permission from Sidell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol*. 1974;7(1):2–6.

comprehension, decreased ability to communicate, or occasional mild confusion. Gross mental aberrations, such as complete disorientation or hallucinations, are not part of the symptom complex.

Studies of Behavioral and Psychological Changes

In one of the earliest studies of the effects of ChE-inhibiting substances,[36] behavioral and psychological changes were reported in 49 of 60 subjects (of whom 50 were normal and 10 had myasthenia gravis) after daily intramuscular doses (1.5–3.0 mg) of DFP. Changes were reported about 1 hour after dose administration. The most prominent CNS effects reported were excessive dreaming (33 subjects); insomnia (29 subjects); and jitteriness, restlessness, increased tension, emotional lability, and tremulousness (29 subjects). The authors noted, without comment, that one subject reported visual hallucinations. Hallucinations are not mentioned elsewhere as an effect of ChE inhibitors. Later, similar effects were reported as sequelae of accidental exposure to nerve agent poisoning.[72]

One report[63] suggests that several workers accidentally exposed to sarin had some behavioral effects. Another report[73] lists "weakness" (actually tiredness), nervousness, and drowsiness as complaints from 16 of 40 workers accidentally exposed to small amounts of nerve agent vapor.

In a series[55] of 49 workers who were accidentally exposed to sarin or tabun (a total of 53 exposures), 13 workers reported sleep disturbances, 12 reported mood changes, and 10 reported easy fatigability. Overall, 51% had CNS effects. The authors pointed out that the complex of CNS symptoms may not fully develop until 24 hours after exposure. The data on blood ChE activities (both RBC-ChE and BuChE) in these workers were scanty. The individual with the greatest ChE inhibition, however, had an RBC-ChE activity of 33% of his personal control value, which suggests that the exposures were not severe. No correlation between the presence or severity of symptoms and the degree of ChE inhibition was seen, and most of the effects of exposure disappeared within 3 days. Systemic atropine was not given to any of these individuals, which suggests that therapy is unnecessary if a paucity of physical signs exists. The authors concluded that mild intoxication by nerve agents may cause psychological disturbances and that these disturbances might have serious consequences to the individuals and to those dependent on their judgment.[55]

In a series[74] of 72 workers exposed to sarin, 2 reported difficulty in concentration, 5 reported mental confusion, 5 reported giddiness, and 4 reported insomnia. All but 2 of these individuals were considered to have been exposed to a small amount of sarin; these 2 were given 2 mg of atropine intramuscularly, and 12 others received atropine orally (0.4–0.8 mg). RBC-ChE ranged from less than 9% to more than 100% of the individual's control activity.

Behavioral changes and whole-blood ChE activities were reported in another study[75] in which VX was placed on the skin of volunteers. Since VX preferentially inhibits RBC-ChE and has relatively little effect on BuChE, the decreases in whole-blood ChE activities were assumed to indicate mainly inhibition of RBC-ChE. In subjects with whole-blood ChE activities of 10% to 40% of control (RBC-ChE activities $\leq$ 20% of control), 30% reported anxiety, 57% had psychomotor depression, 57% had intellectual impairment, and 38% had unusual dreams. Of those with whole-blood ChE activities of 41% to 80% of control (RBC-ChE activities of 20%–40% of control), 8% reported anxiety, 4% had psychomotor depression, 4% had intellectual depression, and 33% had unusual dreams. Nausea and vomiting were the other symptoms noted. Some subjects had both psychological and gastrointestinal effects, with onsets often separated by several hours. Some subjects had symptoms related to only one organ system.

Overall, the onset of signs and symptoms occurred 3.5 to 18 hours after percutaneous exposure, and maximal depression in blood ChE occurred 3 to 8 hours after exposure. However, no measurements were taken between 8 and 24 hours, and the maximal inhibition might have been in this period. (It is not often recognized that there may be a long delay between exposure on the skin and onset of signs or symptoms.) The authors stressed that psychological impairment might occur before the onset of other signs or symptoms or might occur in their absence.[75]

Although the frequency, onset, and duration of each reaction were not noted, some of the behavioral effects reported in the VX subjects were fatigue, jitteriness or tenseness, inability to read with comprehension, difficulties with thinking and expression, forgetfulness, inability to maintain a thought trend, a feeling of being mentally slowed, depression, irritability, listlessness, poor performance on serial 7s and other simple arithmetic tests, minor difficulties in orientation, and frightening dreams. Illogical or inappropriate trends in language and thinking were not noted, nor was there evidence of conceptual looseness. The investigators found no evidence of perceptual distortion resulting in delusions or hallucinations.

A severe, accidental exposure to soman caused one person to become depressed, withdrawn, and subdued, have antisocial thoughts, and sleep restlessly with bad dreams for several days immediately after the exposure (see Exhibit 5-4).[18] He received oral doses of scopolamine hydrobromide on 3 of the following 6 days and was given scopolamine methylbromide, which does not enter the CNS, on the other days to mimic the peripheral effects of the hydrobromide salt, such as dry mouth. On the hydrobromide days, the subject was more spontaneous and alert, less depressed, and slept better; his performance on a simple arithmetic test also improved. Because scopolamine hydrobromide is more effective in the CNS than the methylbromide salt of scopolamine or atropine, it seemed likely that the drug reversed the CNS effects, at least temporarily. The subject's performance on standard psychological tests 16 days after exposure was below that expected for one of his intellectual capabilities, but it improved to his expected level of functioning when he was tested 4 months later and again at 6 months later when he was discharged from further care. The author suggested that the use of scopolamine hydrobromide deserves further evaluation in patients who have these lingering effects while recovering from nerve agent poisoning.

Changes in the ability to perform certain laboratory or field tests after exposure to sarin have been reported. Generally, at the exposures used (C*t*s of 4–14.7 mg•min/m^3), there was some impairment on tasks requiring vision, hand–eye coordination, dexterity, response time, comprehension, and judgment.[76,77] No decrements were found on physical tasks[78] (at a C*t* of 14.7 mg•min/m^3). On a military field exercise,[79] most tasks were performed satisfactorily, if suboptimally, in the daylight. Nighttime performance, however, was difficult, if not downright hazardous.

Electroencephalographic Effects

Information is scanty on the electroencephalographic (EEG) effects in humans who have been severely poisoned by ChE-inhibiting substances. In an early study,[80] DFP, administered intramuscularly daily, caused EEG changes in 19 of 23 subjects (19 normal, 4 with myasthenia gravis). The changes were

- greater-than-normal variations in potential;
- increased frequency, with increased beta rhythm; and
- more irregularities in rhythm and the intermittent appearance of abnormal waves (high-voltage, slow waves; these were most prominent in the frontal leads).

These changes usually followed the onset of CNS symptoms, they could be correlated with decreases of RBC-ChE activity (but not with BuChE decreases), and they were decreased or reversed by atropine 1.2 mg, administered intravenously.

In another study,[81] the EEG of a subject who was severely intoxicated with sarin was recorded after the loss of consciousness but before the onset of convulsions. The recording showed marked slowing of activity, with bursts of high-voltage, 5-Hz waves in the temporofrontal leads. These waves persisted for 6 days despite atropine administration.

In one study[43] in which subjects were exposed to smaller amounts of sarin, the EEG changes coincided with severity of symptoms. With mild symptoms, there was a slight diminution of voltage. Irregularities in rhythm, variation in potential, and intermittent bursts of abnormal waves (slow, elevated-voltage waves) occurred with moderate symptoms. These changes persisted for 4 to 8 days after the disappearance of symptoms and decreased somewhat (decreases in voltage, in irregular frequency and potential, and in slow waves) after administration of atropine 1 mg, administered intravenously.

Long-Term Effects

Long-term effects on the human CNS after poisoning with nerve agents or organophosphate insecticides have been reported.[18,82,83] These reports are based on clinical observations, which occasionally are supported by psychological studies. In general, the behavioral effects have not been permanent but have lasted weeks to several months, or possibly several years.[84]

Necropsy findings from animal studies suggest that there are long-lasting or permanent CNS effects after exposures to lethal or near-lethal amounts of nerve agents. In one study,[85] 264 rats were given approximately 1 LD_{50} of soman. Some animals died shortly after agent administration; others were sacrificed at intervals up to 39 days. In those surviving for 39 days, no neurological sequelae were reported. On microscopic examination of the brains of the deceased animals, neuronal changes similar to those seen after hypoxic encephalopathy were found in some animals, but only in those that had exhibited respiratory distress and repeated or prolonged convulsions.

In another study[86] with a similar protocol, brains of rats were examined 15 to 28 days after the animals were given a single dose of soman. Lesions were seen in all of the animals that had convulsions, in three of four that had tremors but not convulsions, and in none of the others. The author concluded that the convulsions were not necessary for the lesions to occur.[86]

The neuronal degeneration and necrosis seen in the brains of soman-poisoned rats in another study[87] suggested a "hypoxic pattern" or the type of lesion seen after status epilepticus. The lesions were seen only in animals that survived prolonged convulsions, and the authors surmised that the brain damage was seizure mediated.

Although most studies have been with soman, similar damage has been reported after exposure to sarin.[88] Also, in one elegant study,[89] VX was microinjected into specific brain regions. The investigators concluded that neuropathology was not due to a direct neurotoxic effect of the agents on brain neurons, that systemic hypoxia is probably not a mechanism for their toxicity, and that the brain damage produced by nerve agents is probably seizure mediated.

In addition to having morphologically detectable brain lesions, animals surviving severe soman intoxication have been shown to have decrements in performance, as measured on a variety of behavioral tests.[90–92] These decrements lasted for about 4 months, when the last survivors were sacrificed.

There is conflicting evidence regarding the possible role of hypoxia as an etiologic factor in brain damage following seizure activity—whether this activity is caused by nerve agents or other factors. Rats given bicuculline convulsed for 2 hours under controlled conditions. Those given a lower percentage of oxygen in their inspired air to keep the partial pressure of arterial oxygen (Pa_{O_2}) close to 50 mm Hg did not have brain lesions, whereas those with normal air intake and Pa_{O_2} higher than 128 mm Hg developed brain lesions.[93] Although this evidence does not eliminate the possibility of localized hypoxic areas in the brain as a factor in nerve agent-induced damage, it does suggest that systemic hypoxia is not a factor. On the other hand, a similar study[94] (hypoxic rats with bicuculline-induced convulsions that lasted 2 h) suggested that there were slightly more brain lesions in the hypoxic animals than in normoxic animals.

In studies in which cynomolgus[86] or rhesus[95] monkeys were given nearly lethal amounts of soman, the animals that convulsed were later found to have morphologically detectable brain damage. Monkeys that were pretreated with pyridostigmine, given soman, and treated with atropine and 2-PAM Cl in another study[70] had severe and prolonged tremors and convulsions. Although the survival rate was much higher than that for the control group, one might expect that more of the survivors would have brain lesions because of the prolonged seizure activity.

In general, in untreated or inadequately treated nerve agent–poisoned animals, convulsive (and seizure) activity usually stops very shortly after respiration ceases. Often these animals die. Occasionally they recover after some degree of apnea, but in either case, the duration of convulsive and seizure activity is brief. In a few reported cases of severe nerve agent intoxication in humans,[18,63,81] convulsive activity has also been brief. Animals given adequate therapy and, in particular, those given pyridostigmine before exposure to the agent are more likely to recover. They also are more likely to have long and recurrent convulsive episodes, since respiration does not stop. The chance of survival increases but, possibly, at the cost of prolonged or permanent CNS damage.

Therapy

Diazepam, an anticonvulsant of the benzodiazepine family, has been shown to control soman-induced convulsions in monkeys[96] and convulsions induced by other ChE inhibitors in the rabbit.[97,98] There have also been anecdotal reports of its effectiveness in controlling convulsions induced by organophosphate insecticides. In rats, diazepam has been reported to decrease the frequency of convulsions and brain lesions (although, when given without atropine, it did not decrease mortality).[99] When given with 2-PAM Cl, with or without atropine, diazepam reduced the severity, but not the incidence, of brain lesions in soman-poisoned rats.[100]

In another study,[101] three groups of monkeys were given pyridostigmine before soman exposure and were treated with atropine and 2-PAM Cl after exposure. One group was also given diazepam, the second was given midazolam, and the third (the control group) was given water. The incidence of tremors decreased in the anticonvulsant-treated animals, and convulsions were absent in these groups. Overall, the brain lesions in the treatment groups in this study were less severe than those seen in animals in a previous study[95] in which animals had received neither pretreatment nor treatment. Although the occurrence of brain lesions in most brain areas was lower in the anticonvulsant-treated

groups than in the control group, the difference was statistically significant ($P < .05$) for only one of these five brain areas studied. Lesions occurred more frequently ($P < .05$) in the frontal cortex in the diazepam-treated group than in the other groups. The reason for this finding and its physiological significance were not apparent to the investigators.

At a workshop[102] on this topic, many investigators in the field reviewed and discussed findings and future avenues for research. It was generally agreed that brain lesions did not occur if convulsions lasted less than 45 minutes, and that brain damage was found if convulsions lasted longer than 45 minutes. This distinction is not apparent in most reports, which specify only that convulsions were "prolonged" or "repeated."

A report[103] notes that brain damage after convulsions was first reported over a century ago, and that the relationship between seizure activity and brain damage has been the subject of numerous studies in past decades. For example, well-oxygenated rats had lesions after 30 minutes of flurothyl-induced convulsions[104]; similar results were found using another volatile convulsant gas in rats.[105] Similarly, baboons that had convulsions for 82 to 299 minutes after bicuculline administration had brain damage.[106] These and other studies, such as that by McDonough and associates,[89] suggest that the brain damage is not caused by the agent per se, but rather by the prolonged seizure and associated disturbances.

The efficacy of diazepam in stopping seizures is generally accepted, and there is evidence that the drug also reduces brain damage. Rats given bicuculline had convulsions for 1 hour; the convulsions were then terminated with diazepam. Rats sacrificed 5 minutes later had fewer brain lesions than did those sacrificed immediately after the cessation of the convulsion. Rats that recovered longer and were sacrificed 2 hours after termination of the convulsion had even less brain damage.[107]

Most reports in the clinical literature recommend stopping the convulsion within 1 hour, using drastic measures, such as hypothermia and barbiturate coma, if necessary.[108] The mortality of status epilepticus (usually defined as a convulsion lasting 60 min, or a series of convulsions lasting 60 min without consciousness intervening) is said to be 6% to 30%. Moreover, twice that number of victims acquire irreversible neurological deficits as a result of status epilepticus.[108] (In a study of children, permanent deficits were found to occur in 34%.[109]) These data emphasize the need for an effective anticonvulsant.

Soldiers are issued three MARK I kits (Figure 5-5). Each MARK I kit contains two autoinjectors: an AtroPen containing 2 mg of atropine in 0.7 mL of diluent, and a ComboPen containing 600 mg of 2-PAM Cl in 2 mL of diluent (autoinjectors and their contents manufactured by Survival Technology, Rockville, Md.). During the Persian Gulf War, the U.S. military also issued an autoinjector containing 10 mg of diazepam to all military personnel. This ComboPen was not intended for self-use, but rather for use by a buddy when a soldier exhibited severe effects from a nerve agent. The buddy system was used because any soldier able to self-administer diazepam does not need it. Medics and unit lifesavers were issued additional diazepam autoinjectors and could administer two additional doses at 10-minute intervals to a convulsing casualty. Current policy states that diazepam is given following the third MARK I when three MARK I kits are given at one time. The contents and use of MARK I kits are further described throughout this chapter.

Cardiovascular System

Few data on the cardiovascular effects of nerve agents in humans exist. In mild-to-moderate intoxi-

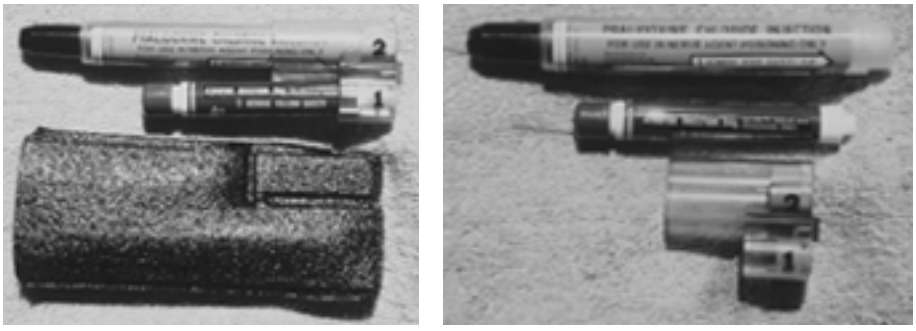

Fig. 5-5. The MARK I kit with its two autoinjectors: the AtroPen (containing atropine), labeled 1, and the ComboPen (containing 2-pyridine aldoxime methyl chloride, 2-PAM Cl), labeled 2. (**a**) The two unused injectors in the safety clip, and the black carrier. (**b**) The used injectors and empty safety clip.

cation from nerve agents, blood pressure may be elevated, presumably because of cholinergic stimulation of ganglia or other factors, such as stress reaction.

Arrhythmias

After nerve agent exposure, the heart rate may decrease and some atrial-ventricular (A-V) heart block (first-, second-, or third-degree) with bradycardia (personal observation) may occur because of the stimulation of the A-V node by the vagus nerve. In some cases, an increase in heart rate may occur because of stress, fright, or some degree of hypoxia. Since the initiation of treatment is of great urgency in severely intoxicated patients, electrocardiograms (ECGs) have not been done before administration of atropine. However, if possible, an ECG should be done before drugs are given if the procedure will not delay therapy. In normal subjects, atropine may cause a very transient A-V dissociation before the onset of bradycardia (which precedes the familiar tachycardia), and ChE-inhibiting substances may cause bradycardia and A-V block. For reasons noted above, these transient rhythm abnormalities have not been recorded in patients with nerve agent intoxication. These rhythm disturbances are probably not important clinically.

Reports of patients exposed to pesticides and the results of animal studies provide additional information about cardiovascular reactions to nerve agents. In one study,[110] dogs exposed to lethal amounts of sarin vapor had idioventricular rhythms within minutes after exposure; following atropine therapy, some of the dogs had third- and first-degree heart blocks before a normal rhythm returned. In another study,[111] conscious dogs had few cardiac rhythm changes after sublethal doses (0.25–0.5 LD_{50}, administered subcutaneously) of VX. Four of five anesthetized dogs receiving a 1-LD_{50} dose had arrhythmias, including first-degree heart block and premature ventricular complexes; one had torsade de pointes (a type of ventricular tachycardia). Cardiac arrhythmias are not uncommon in humans after organophosphate pesticide poisoning.[112]

Dogs were instrumented to examine the cardiac changes occurring for a month after intravenous administration of 2 LD_{50} of soman.[113] Atropine and diazepam were administered shortly after soman exposure to control seizure activity. During the study period, there was an increased frequency of episodes of bradycardia with ventricular escape, second- and third-degree heart block, and independent ventricular activity (single premature beats, bigeminy, or runs of ventricular tachycardia).

In a similar study,[114] rhesus monkeys were given the standard military regimen of pyridostigmine before exposure to soman (1 LD_{50}, administered intramuscularly), and atropine and 2-PAM Cl after the agent. The monkeys were monitored continuously for 4 weeks. Except for the period immediately after agent administration, the incidence of arrhythmias was the same as or less than that observed during a 2-week baseline period.

Torsade de pointes has been reported after nerve agent poisoning in animals[111] and after organophosphate pesticide poisoning in humans.[115] Torsade de pointes is a ventricular arrhythmia, usually rapid, of multifocal origin, which on ECGs resembles a pattern midway between ventricular tachycardia and fibrillation. It is generally preceded by a prolongation of the QT interval, it starts and stops suddenly, and it is refractory to commonly used therapy. It was first described as a clinical entity in the late 1960s; undoubtedly it was seen but called by another name in experimental studies with nerve agents before then.

Ventricular fibrillation, a potentially fatal arrhythmia, has been seen after administration of a ChE inhibitor and atropine. It can be precipitated by the intravenous administration of atropine to an animal that has been rendered hypoxic by administration of a ChE inhibitor.[116,117] Although this complication has not been reported in humans, atropine should not be given intravenously until the hypoxia has been at least partially corrected.

Heart Rate

Although it is frequently stated that a patient intoxicated with a nerve agent will have bradycardia, this is not borne out by clinical data. In a review of the records of 199 patients seen at the Edgewood Arsenal Toxic Exposure Aid Station for mild-to-moderate nerve agent exposure (one or more definite signs or symptoms of nerve agent intoxication, such as miosis or a combination of miosis with dim vision or a tight chest), 13 presented with heart rates less than 64 beats per minute. There were 13 patients with heart rates of 64 to 69 beats per minute, 63 with heart rates of 70 to 80, 41 with heart rates of 81 to 89, 38 with heart rates of 90 to 99, and 31 with heart rates higher than 100. A heart rate of 64 to 80 beats per minute is considered normal in adults.[118] Thus, 13 patients (6.5%) had low heart rates, and 110 patients (55%) had high heart rates; (69 of these patients [35%] had heart rates ≥ 90).

Reports of the heart rates of patients severely

intoxicated by insecticides vary. In a report[119] describing 10 patients (9 of whom had moderate-to-severe impairment of consciousness), 7 presented with heart rates over 100 and the other 3 had heart rates over 90 (5 had a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or both). In another report,[120] the heart rates of 3 unconscious patients were slow (1 had cardiac arrest). In a comprehensive review of organophosphate poisoning,[51] 2 acutely ill, unconscious patients were described; 1 had a heart rate of 108 beats per minute and the other, 80. The authors of the study pointed out that cardiovascular function is usually maintained until the terminal stage and that blood pressure and heart rate increase in the acute stage but may decline later. Heart rate was not listed in their tabulation of signs and symptoms.

GENERAL TREATMENT PRINCIPLES

The principles of treatment of nerve agent poisoning are the same as they are for any toxic substance exposure: namely, terminate the exposure; establish or maintain ventilation; administer an antidote, if one is available; and correct cardiovascular abnormalities.

Most importantly, medical care providers or rescuers must protect themselves from contamination. If the caregiver becomes contaminated, there will be one more casualty and one fewer rescuer. Protection of the rescuer can be achieved by physical means, such as masks, gloves, and aprons, or by ensuring that the casualty has been thoroughly decontaminated. The importance of casualty decontamination should be obvious, but, unfortunately, it is often forgotten or overlooked. There were reports that in several instances during the Iran–Iraq War (1981–1988), incompletely decontaminated mustard casualties who were transported to European medical centers for further care caused contamination of others, who then also became casualties.

This section discusses the general principles of treating nerve agent poisoning. The specific treatment of casualties in the six exposure categories (suspected, minimal, mild, moderate, moderately severe, and severe) is addressed in the next section.

Terminating the Exposure

Decontamination is performed for two reasons:

1. to prevent further absorption of the agent by the casualty or further spread of the agent on the casualty, and
2. to prevent spread of the agent to others, including medical personnel, who must handle or who might come into contact with the casualty.

Because of the small amount of nerve agent needed to cause death and because of the short time (10–15 min) in which a lethal amount will cause severe effects in an untreated casualty, it is unlikely that a living nerve agent–poisoned casualty with nerve agent on his skin will be brought to a medical care facility. To successfully reduce damage to the casualty, decontamination must be performed within minutes after exposure. The only decontamination that prevents or significantly reduces damage from a chemical agent, whether a nerve agent or another agent, is that done within the first several minutes: *self-decontamination*.

The importance of rapid self-decontamination cannot be overemphasized and must be clearly understood by anyone who might be exposed to chemical agents. Because the skin absorbs most chemical agents rapidly and because of evaporation (even "persistent" agents, such as VX and mustard, evaporate from skin rather quickly), it is unlikely that there will be a significant amount of agent on the skin by the time the casualty reaches a medical treatment facility. However, agent may be in areas, such as in hair or on clothing, where it will not be readily absorbed percutaneously. *Skin decontamination is not necessary after exposure to nerve agent vapor*.

If vapor is the only exposure source, the exposure can be terminated by putting a protective mask on the casualty or by moving him to an environment free of toxic vapor (eg, by moving the casualty outside and sealing the doors if the vapor is in a room or building). The standard M40 (or M17A2) protective mask will protect against any likely field concentration of nerve agent vapor for days.

Liquid agent on the skin or clothing should be physically removed and detoxified by chemical degradation or neutralization. Nerve agents penetrate clothing; mere removal of contaminated apparel is not adequate since some agents may reach the skin before the clothing is removed. If the contamination is localized, cutting out the affected section of clothing (leaving very wide margins) may be adequate. If there is doubt, however, all cloth-

ing should be removed. The underlying skin should then be decontaminated thoroughly.

The M291 decontamination kit contains charcoal and sorptive resins; the agent is physically removed and adsorbed. The M258A1 is a standard decontamination kit that contains two moistened towelettes. One is intended for use with the G agents, and the other with VX and mustard. Since the agent probably would not be identified at the time of exposure in the field, both towelettes should be used to physically remove the chemical agent by blotting, not wiping, it; the towelettes also aid in decontamination by chemically neutralizing the agent, although this chemical reaction is slow. (See Chapter 15, Decontamination, and Chapter 16, Chemical Defense Equipment, for details about the decontamination kits.)

A solution that releases chlorine, such as household bleach (5% sodium hypochlorite) or a solution that is sufficiently alkaline to neutralize the agent, such as dilute hydroxide, can also be used for physical removal and chemical neutralization of a chemical agent. Because of the potential for skin damage from 5% hypochlorite, the current military procedure is to use 0.5% hypochlorite for skin decontamination. Dilute hydroxide and the contents of the M258A1 kit are damaging to the skin, however, and should be thoroughly rinsed off.

Water is also a decontaminant since, when used in large amounts, it physically removes and dilutes chemical agents. (Most agents hydrolyze to some degree in water, but hydrolysis usually takes hours to days.) If used alone, water is not ideal; however, if nothing else is available, flushing with large amounts of water to physically remove the chemical agent is satisfactory. Water should be used to wash off the other decontaminants. Commonly available products (such as tissue paper and flour) that can help remove or adsorb the agent should be used if other decontaminants are not available.[121]

Ventilatory Support

Ventilatory support is a necessary aspect of therapy if a casualty with severe respiratory compromise is to be saved. Antidotes alone may be effective in restoring ventilation and saving lives in some instances; in animal studies,[122,123] antidotes alone, given intramuscularly at the onset of signs, were adequate to reverse the effects of agent doses of about 3 LD_{50}, but their effectiveness was greatly increased with the addition of ventilation. Pyridostigmine, given as pretreatment and followed by the current therapy after challenges with higher amounts of two agents, appears to prevent apnea (see Chapter 6, Pretreatment for Nerve Agent Exposure).

Impairment of breathing is an early effect of exposure to nerve agent vapor or aerosol. When the exposure is small, the casualty may have mild to severe dyspnea, with corresponding physical findings, and the impairment will be reversed by the administration of atropine. If the distress is severe and the casualty is elderly or has pulmonary or cardiac disease, the antidote may be supplemented by providing oxygen by inhalation. In most other circumstances, supplementation with oxygen is unnecessary.

Severely exposed casualties lose consciousness shortly after the onset of effects, usually before any signs of respiratory compromise. They have generalized muscular twitching or convulsive jerks and may initially have spontaneous but impaired respiration. Breathing ceases completely within several minutes after the onset of exposure in a severely poisoned person who has not been pretreated with pyridostigmine.

Assisted ventilation may be required to supplement gasping and infrequent attempts at respiration, or it may be required because spontaneous breathing has stopped. In addition to a decrease in central respiratory drive, weakness or paralysis of thoracic and diaphragmatic muscles, and bronchospasm or constriction, there are copious secretions throughout the airways. These secretions tend to be thick, mucoid, and "ropy," and may plug up the airways. Postural drainage can be used, and frequent and thorough suctioning of the airways is necessary if ventilation is to be successful. In one instance, efforts to ventilate a severely apneic casualty were markedly hindered for 30 minutes until adequate suction was applied to remove thick mucoid plugs.[63]

Initially, because of the constriction or spasm of the bronchial musculature, there is marked resistance to attempts to ventilate. Pressures of 50 to 70 cm H_2O or greater may be needed. After the administration of atropine, resistance decreases to 40 cm H_2O or lower, and the secretions diminish (although they may thicken), creating less obstruction to ventilatory efforts.

There are numerous mechanical devices, including sophisticated ventilators, that can be used to provide ventilatory assistance in an apneic casualty. None of these is available to the soldier or his buddy, and only a few—the mask-valve-bag venti-

lation device, the RDIC (resuscitation device, individual, chemical), and a simple ventilator—are available at the battalion aid station. Whatever device is used, it must be able to overcome the initial high resistance in the airways. If a casualty is apneic or has severe respiratory compromise and needs assisted ventilation, then endotracheal intubation, which will enable better ventilation and suction of secretions, can and should be attempted.

Mouth-to-mouth ventilation might be considered by a soldier who wants to assist an apneic buddy when no aid station is nearby. A major drawback is the likelihood of contamination. Before even considering this method, the rescuer should be sure that there is no vapor hazard, which is not always possible, and that there is no liquid contamination on the individual to be ventilated. The expired breath of the casualty is a lesser hazard. Studies[124–126] involving sarin have shown that only 10% or less of inspired nerve agent is expired, and that the toxicant is expired immediately after inspiration of the agent.

The Schäfer method of assisted ventilation (ie, gentle, intermittent pressure applied to the lower part of the thorax of a prone person to mimic breathing) was formerly used in severely poisoned individuals until other means became available. Generally, this is not a reliable method of ventilation even in an individual with normal airways.

In summary, spontaneous respiration will stop within several minutes after onset of effects caused by exposure to a lethal amount of nerve agent. Antidotes alone are relatively ineffective in restoring spontaneous respiration. Attempts at ventilation are hindered by the high resistance of constricted bronchiolar muscles and by copious secretions, which may be thick and plug the bronchi. Ventilatory assistance may be required briefly (20–30 min) or for a much longer period. In several instances, assistance was required for 3 hours[18,63]; this seems to be the longest reported use of ventilation.

Atropine Therapy

The antagonism between the ChE-inhibiting substance physostigmine and a cholinergic blocking substance has been recognized for well over a century.[127] In the early 1950s, atropine was found to reduce the severity of effects from ChE-inhibitor poisoning, but it did not prevent deaths in animals exposed to synthetic ChE-inhibiting insecticides.[128]

Cholinergic blocking substances act by blocking the effects of excess acetylcholine at muscarinic receptors. Acetylcholine accumulates at these receptors because it is not hydrolyzed by ChE when the enzyme is inactivated by an inhibitor. Thus, cholinergic blocking substances do not block the direct effect of the agent (ChE inhibition); rather, they block the effect of the resulting excess ACh.

Many cholinergic blocking substances have been tested for antidotal activity. Among the findings are the following:

- Almost any compound with cholinergic blocking activity has antidotal activity.
- Atropine and related substances reduce the effects of the ChE inhibitors, primarily in those tissues with muscarinic receptor sites.
- Antidotal substances with higher lipoid solubility, which penetrate the CNS more readily, might be expected to have greater antidotal activity, since some of the more severe effects of ChE inhibitor poisoning (such as apnea and seizures) are mediated in the CNS.

  For example, the combination of benactyzine and atropine was shown to be more effective than atropine alone in reducing lethality from sarin[128]; 3-quinuclidinyl benzilate (BZ, also called QNB; see Chapter 11, Incapacitating Agents) is an excellent antidote. Benactyzine was part of a mixture (plus atropine and *N*,*N*′-trimethylenebis-[pyridine-4-aldoxime bromide] [TMB4]) fielded as a nerve agent antidote (known as TAB) for several years in the late 1970s. However, these substances have CNS effects in the absence of nerve agents; this was one of the reasons that this mixture was withdrawn.

In the late 1940s, atropine was chosen as the standard antidote; despite extensive searches for other antidotes since, it has remained the standard. A dose of 2 mg was chosen for self- or buddy-administration (the AtroPen automatic injector included in the MARK I kit contains 2 mg) because it reverses the effects of nerve agents, the associated side effects of a dose this size can be tolerated, and reasonably normal performance can be maintained by the individual receiving it. The rationale for this choice of dose was expressed (in the unclassified portion of a classified document) as follows:

> The dose of atropine which the individual serviceman can be allowed to use must be a compromise between the dose which is therapeutically desir-

able and that which can be safely administered to a nonintoxicated person. Laboratory trials have shown that 2 mg of atropine sulfate is a reasonable amount to be recommended for injection by an individual and that higher doses may produce embarrassing effects on troops with operational responsibilities.

When given to a normal individual (one without nerve agent intoxication), a dose of 2 mg of atropine will cause an increase in heart rate of about 35 beats per minute (which usually is not noticed by the recipient), a dry mouth, dry skin, mydriasis, and some paralysis of accommodation. Most of these effects will dissipate by 4 to 6 hours, but near vision may be blurred for 24 hours, even in healthy young men. The decrease in sweating caused by 2 mg of atropine is a major, potentially harmful side effect that may cause some people who work in the heat to become casualties. For example, when 35 soldiers were given 2 mg of atropine and asked to walk for 115 minutes at 3.3 mph at a temperature of about 83°F (71°F wet bulb), more than half dropped out because of illness or were removed from the walk because of body temperature of 103.5°F or above; on another day, without atropine, they all successfully completed the same march.[129]

The 6 mg of atropine contained in the three injectors given each soldier may cause mild mental aberrations (such as drowsiness or forgetfulness) in some individuals if administered in the absence of nerve agent intoxication. Atropine given intravenously to healthy young people causes a maximal increase in the heart rate in 3 to 5 minutes, but other effects (such as drying of the mouth and change in pupil size) appear later. In one study,[130] when atropine was administered with the AtroPen, the greatest degree of bradycardia occurred at 2.5 minutes (compared with 4.3 min when administered by standard needle-and-syringe injection); a heart rate increase of 10 beats per minute occurred at 7.9 minutes (vs 14.7 min with needle-and-syringe injection); and maximal tachycardia (an increase of 47 beats per min) occurred at 34.4 minutes (compared with an increase of 36.6 beats per min at 40.7 min with needle-and-syringe injection).

Thus, the autoinjector is not only more convenient to use than the needle and syringe, but its use causes more rapid absorption of the drug. Needle-and-syringe delivery produces a "glob" or puddle of liquid in muscle. The AtroPen, on the other hand, sprays the liquid throughout the muscle as the needle goes in. The greater dispersion of the AtroPen deposit results in more rapid absorption. It has not been determined whether the onset of beneficial effects in treating nerve agent intoxication corresponds to the onset of bradycardia, the onset of tachycardia, or to other factors.

When administered in an adequate amount, atropine reverses the effects of the nerve agent in tissues that have muscarinic receptor sites. It decreases secretions and reverses the spasm or contraction of smooth muscle. The mouth dries, secretions in the mouth and bronchi dry, bronchoconstriction decreases, and gastrointestinal musculature will be less hyperactive. However, unless given in very large doses, intravenous or intramuscular atropine does not reverse miosis caused by nerve agent vapor in the eyes. A casualty with miosis alone should not be given atropine, therefore, and pupil size should not be used to judge the adequacy of atropine dosage. Whether atropine controls convulsions in humans is unclear.

The amount of atropine to administer is a matter of judgment. In a conscious casualty with mild-to-moderate effects who is not in severe distress, 2 mg of atropine should be given intramuscularly at 5- to 10-minute intervals until dyspnea and secretions are minimized. Usually no more than a total dose of 2 to 4 mg is needed. In an unconscious casualty, atropine should be given (*a*) until secretions are minimized (those in the mouth can be seen and those in the lungs can be heard by auscultation) and (*b*) until resistance to ventilatory efforts is minimized (atropine decreases constriction of the bronchial musculature and airway secretions). If the casualty is conscious, he will report less dyspnea, and if assisted ventilation is underway, a decrease in airway resistance will be noted. Secretions alone should not be the reason for administering more atropine if the secretions are diminishing and are not clinically significant. Mucus blocking the smaller airways may remain a hindrance despite adequate amounts of atropine. In severe casualties (unconscious and apneic), 5 to 15 mg of atropine has been used before spontaneous respiration resumed and the casualty regained consciousness (which occurred 30 min to 3 h after exposure).[18,63] Several recovering casualties have had non–life-threatening adverse effects (such as nausea and vomiting) 24 to 36 hours after exposure for which atropine was administered (personal observation).[18] However, there would appear to be no reason to give atropine routinely in this period.

In contrast, much larger amounts of atropine (500–1,000 mg) have been required in the initial 24 hours of treatment of individuals severely poisoned by organophosphorus pesticides.[131–133] *Medical care providers must recognize that the amount of atropine*

needed for treatment of insecticide poisoning is different from the amount needed for treatment of nerve agent poisoning. Pesticides may be sequestered in the body or metabolized at a slower rate than nerve agents; whatever the reason, they continue to cause acute cholinergic crises for a much longer period (days to weeks).

The goal of therapy with atropine should be to minimize the effects of the agent (ie, to remove the casualty from a life-threatening situation and to make him comfortable), which may not require complete reversal of all of the effects (such as miosis). However, in a casualty with severe effects, it is better to administer too much atropine than too little. Too much atropine does far less harm than too much unantagonized nerve agent in a casualty suffering severe effects. However, a moderately dyspneic casualty given atropine 2 mg, administered intramuscularly, will report improvement within 5 minutes. A caregiver should resist the temptation to give too much atropine to a walking, talking casualty with dyspnea. In general, the correct dose of atropine for an individual exposed to a nerve agent is determined by the casualty's signs and symptoms, the route of exposure (vapor or liquid), and the amount of time elapsed since exposure.

Atropine Therapy After Inhalational Exposure to Vapor

After vapor exposure, the effects of nerve agents appear very quickly and reach their maximum activity within seconds or minutes after the casualty is removed from or protected against the vapor. In what were apparently high concentrations of nerve agent vapor, two individuals collapsed, unconscious, almost immediately after taking one or two breaths, and 4 to 5 minutes later they were flaccid and apneic.[18,63] Even at very low concentrations, maximal effects occur within minutes of termination of exposure. Because effects develop so rapidly, antidotal therapy should be more vigorous for a casualty seen during or immediately after exposure than for a casualty seen 15 to 30 minutes later. For example, if a soldier's buddy in the field or a coworker in a laboratory suddenly complains of dim vision in an environment suspected of containing nerve agent vapor, the buddy or worker should immediately administer the contents of one MARK I antidote kit. There may be continuing exposure before the casualty can exit the environment or don a mask, or the effects from the exposure already absorbed may continue to develop for several minutes. On the other hand, if the casualty is seen at the medical aid station (installation or field) 15 to 30 minutes after the vapor exposure has terminated, an antidote is not needed if miosis is the only sign (atropine given intramuscularly has very little effect on miosis). Effects caused by nerve agent vapor will not progress after this time.

As a general rule, if a casualty is seen immediately after exposure from vapor only, the contents of one MARK I kit should be given if miosis is the only sign, the contents of two kits should be administered immediately if there is any dyspnea, and the contents of three kits should be given for severe dyspnea or any more-severe signs or symptoms. When seen 15 to 30 minutes after an exposure to vapor alone, the casualty should receive no antidote if miosis is the only sign, the contents of one MARK I kit for mild or moderate dyspnea, the contents of two kits for severe dyspnea (obvious gasping), and the contents of three kits and diazepam (with additional atropine, but no more oxime) if there are more serious signs (such as collapse or loss of consciousness). If dyspnea is the most severe symptom, relief should begin within 5 minutes, and the drugs should not be repeated until this interval has passed. Remember that the aggressive therapy given immediately after the onset of effects is not for those early effects per se (eg, atropine is relatively ineffective against miosis), but is in anticipation of more-severe effects within the following minutes.

Atropine Therapy After Dermal Exposure to Liquid

The therapy for an individual whose skin has been exposed to nerve agent is less clear. The onset of effects is rarely immediate; they may begin within minutes of exposure or as long as 18 hours later. As a general rule, the greater the exposure, the sooner the onset; and the longer the interval between exposure and onset of effects, the less severe the eventual effects will be. Effects can begin hours after thorough decontamination; the time of onset may be related to the duration of time the agent was in contact with the skin before decontamination.

The problem with treating dermal exposure is not so much *how* to treat a symptomatic casualty as *whether* to treat an asymptomatic person who has had agent on the skin. Medical personnel usually have little or no information about the exposure incident, because the casualty often does not know the duration or amount of exposure.

The first effects of agent on the skin are localized sweating and fasciculations of underlying

musculature (rippling), which usually are not observed. If these effects are noted, however, the casualty should immediately self-administer or be given the contents of one MARK I kit. These signs indicate that the chemical agent has penetrated the skin layers.

In general, an asymptomatic person who has had skin contact with a nerve agent should be kept under medical observation, because effects may begin precipitately hours later. Caregivers should not administer the contents of a MARK I kit to an asymptomatic person, but should wait for evidence of agent absorption. However, if an individual is seen minutes after a definite exposure to a large amount of nerve agent on the skin ("large" is relative; the LD_{50} for skin exposure to VX is only 6–10 mg, which is equivalent to a single drop 2–3 mm in diameter), there may be some benefit in administering antidotes before the onset of effects. When the occurrence of exposure is uncertain, the possible benefits of treatment must be weighed against the side effects of antidotes in an unpoisoned individual.

Antidotes should be administered until ventilation is adequate and secretions are minimal. In a mildly to moderately symptomatic individual who is complaining of dyspnea, relief is usually obtained with 2 or 4 mg of atropine (the amount of atropine in one or two MARK I kits). In a severely exposed person who is unconscious and apneic or nearly apneic, at least 6 mg of atropine (the amount in three MARK I kits), and probably more, should be administered initially, and ventilatory support should be started. Atropine should be continued at appropriate intervals until the casualty is breathing adequately with a minimal amount of secretions in the mouth and lungs. The initial 2 or 4 mg has proven adequate in conscious casualties. Although 6 to 15 mg has been required in apneic or nearly apneic casualties, the need for continuing atropine has not extended beyond 2 to 3 hours (although distressing but not life-threatening effects, such as nausea and vomiting, have necessitated administering additional atropine in the following 6–36 h). This is in contrast to the use of atropine to treat intoxication by organophosphorus insecticides, which may cause cholinergic crises (such as an increase in secretion and bronchospasm) for days to weeks after the initial insult.[131–133]

Oxime Therapy

Oximes are nucleophilic substances that reactivate the organophosphate-inhibited ChE (the phosphorylated enzyme) by removing the organophosphoryl moiety. There are limitations to oxime therapy, however.

Mechanism of Action

After the organophosphorus compound attaches to the enzyme to inhibit it, one of the following processes may occur:

- the enzyme may be spontaneously reactivated by hydrolytic cleavage, which breaks the organophosphoryl–ChE bond, reactivating the enzyme; or
- the organophosphoryl–ChE bond may "age," or become resistant to reactivation by water or oxime.

Both of these processes are related to the size of the alkyl group attached to the oxygen of the organophosphorus compound, the group attached to the first carbon of this alkyl group, and other factors. Once the organophosphoryl–enzyme complex ages, it cannot be broken by an oxime. (Further discussion of the chemical process can be found elsewhere; for a brief discussion, see Chapter 6, Pretreatment for Nerve Agent Exposure; for more detailed information, see Koelle.[11]) Oxime therapy is not effective after aging occurs.

Because the nerve agents differ in structure, their rates of spontaneous reactivation and aging differ. For example, when complexed with VX, RBC-ChE spontaneously reactivates at a rate of roughly 0.5% to 1% per hour for about the first 48 hours; the VX–enzyme complex ages very little during this period.[42,45,83] The soman–enzyme complex does not spontaneously reactivate; the half-time for aging is about 2 minutes. The half-time for aging of the sarin–RBC-ChE complex is about 5 hours, and a small percentage (5%) of the enzyme undergoes spontaneous reactivation.[83] The half-time for aging of the tabun–enzyme complex is somewhat longer. (See Table 6-1 in Chapter 6, Pretreatment for Nerve Agent Exposure, for nerve agent–aging times.)

In the mid 1950s, Wilson and coworkers reported that hydroxamine reactivated organophosphoryl-inhibited ChE faster than water did,[134] and later reported that an oxime (pyridine-2-aldoxime methiodide [2-PAMI]) was far more effective than hydroxamine in reactivating the enzyme.[135]

The oximes differ in their required doses, their toxicity, and their effectiveness (for example, TMB4 is more effective against tabun poisoning than is 2-PAM Cl). After thorough study of many of these

compounds, 2-PAM Cl was chosen for use in the United States. The choice was made because of research in both the civilian and military sectors and also because of the demonstrated efficacy of 2-PAM Cl in treating organophosphorus insecticide poisoning.[136–142] At present, the only oxime approved by the Food and Drug Administration for use in the United States is 2-PAM Cl. The methanesulfonate salt of pralidoxime (P2S) is the standard oxime in the United Kingdom, whereas TMB4 and Toxogonin (obidoxime) are used in other European countries.

Since oximes reactivate the ChE inhibited by a nerve agent, they might be expected to completely reverse the effects caused by nerve agents. However, because nerve agents possibly produce biological activity by mechanisms other than inhibition of ChE or because of reasons not understood, oximes are relatively ineffective in reversing effects in organs with muscarinic receptor sites. They are much more effective in reversing nerve agent–induced changes in organs with nicotinic receptor sites. In particular, when oximes are effective (ie, in the absence of aging), they decrease the abnormality in skeletal muscle, improving strength and decreasing fasciculations.

Dosage

The therapeutic dosage of 2-PAM Cl has not been established, but indirect evidence suggests that it is 15 to 25 mg/kg. The effective dose depends on the nerve agent, the time between poisoning and oxime administration, and other factors. An early study[143] showed that a plasma concentration of about 4 µg/mL in blood reversed the sarin-induced neuromuscular block in anesthetized cats; for years this concentration was generally accepted as being therapeutic for sarin. There are few data to support or disprove this contention. The 2-PAM Cl administered with the ComboPen autoinjector (600 mg) produces a maximal plasma concentration of 6.5 µg/mL when injected intramuscularly in the average soldier (8.9 mg/kg in a 70-kg man).[130]

Different doses of 2-PAM Cl were administered (with atropine) in several studies. In sarin-poisoned rabbits, the protective ratio (PR: the ratio of the LD_{50} with treatment to the LD_{50} without treatment) increased from 25 to 90 when the intravenous dose of 2-PAM Cl increased from 5 mg/kg to 10 mg/kg[144]; the PR increased from 1.6 to 4.2 when the intramuscular dose of 2-PAM Cl increased from 30 mg/kg to 120 mg/kg in sarin-poisoned rats[122]; and the PR increased from 1.9 to 3.1 when the intramuscular dose of 2-PAM Cl increased from 11.2 mg/kg to 22.5 mg/kg in VX-poisoned rabbits.[123] (In the first two studies, the antidote was given immediately after the nerve agent; in the third, it was given at the onset of signs. No ventilatory support was used.) In humans, when 2-PAM Cl was administered intravenously 1 hour after sarin, a dose of 10 mg/kg reactivated 28% of the RBC-ChE, and doses of 15 or 20 mg/kg reactivated 58% of the enzyme. When given 3 hours after sarin, 5 mg/kg of 2-PAM Cl reactivated only 10% of the inhibited RBC-ChE, and 10 mg/kg or more reactivated more than 50%. When 2-PAM Cl was given at times from 0.5 to 24 hours after VX, doses of 2.5 to 25 mg/kg were found to reactivate 50% or more of the inhibited enzyme.[83]

For optimal therapy, 2-PAM Cl should be given intravenously, but usually this is not possible in the field. Even at small doses (2.5–5.0 mg/kg), the drug, when given intravenously in the absence of nerve agent poisoning, may cause transient effects, such as dizziness and blurred vision, which increase as the dose increases. Transient diplopia may occur at doses higher than 10 mg/kg. These effects, if they occur, are insignificant in a casualty poisoned with a ChE-inhibiting substance. Occasionally, nausea and vomiting may occur. The most serious side effect is hypertension, which is usually slight and transient at intravenous doses of 15 mg/kg or less, but may be marked and prolonged at higher doses.[145] 2-PAM Cl is commercially available as the cryodesiccated form (Protopam Chloride, manufactured by Wyeth-Ayerst Laboratories, Philadelphia, Pa.) in vials containing 1 g, or about 14 mg/kg for a 70-kg person. Blood pressure elevations greater than 90 mm Hg systolic and 30 mm Hg diastolic may occur after administration of 45 mg/kg, and the elevations may persist for several hours.[145] Giving the oxime slowly (over 30–40 min) may minimize the hypertensive effect, and the hypertension can be quickly but transiently reversed by phentolamine 5 mg, administered intravenously (Figure 5-6).

2-PAM Cl is rapidly and almost completely excreted unchanged by the kidneys: 80% to 90% of an intramuscular or intravenous dose is excreted in 3 hours,[146] probably by an active tubular excretory mechanism (its renal clearance is close to that of *p*-aminohippurate[147]), with a half-time of about 90 minutes.[146] Both clearance and amount excreted are decreased by heat, exercise, or both.[148] Thiamine also decreases excretion (presumably by blocking tubular excretion), prolongs the plasma half-life, and increases the plasma concentration for the duration of thiamine activity[147–150]; some[151] question the therapeutic benefit of thiamine, however.

Fig. 5-6. An infusion of 25 mg/kg of pralidoxime chloride (2-PAM Cl) over about 25 minutes produces marked hypertension, which is rapidly but transiently reversed by phentolamine 5 mg. The mean blood pressure is the diastolic plus one third of the difference between the systolic and the diastolic. Reprinted with permission from Sidell FR. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. New York, NY: Academic Press; 1992: 181.

An early clinical report[152] on the use of 2-PAM Cl in insecticide-poisoned persons indicated that the oxime reversed the CNS effects of the poison (eg, patients regained consciousness and stopped convulsing shortly after the oxime was given). However, other early investigators found no oxime in the brain of animals[153,154] or the cerebrospinal fluid of humans[155] after experimental administration of 2-PAM Cl. Other investigators[71,156] found small amounts of 2-PAM Cl or reversal of the brain ChE inhibition in brains of animals poisoned with organophosphorus compounds.

Administration

Initially, an oxime should be administered with atropine. In cases of severe exposure, the contents of three MARK I kits should be administered; if the kits are not available, then oxime 1 to 1.5 g should be administered intravenously over a period of 20 to 30 minutes or longer. Additional atropine should be given to minimize secretions and to reduce ventilatory problems, thereby relieving the casualty's distress and discomfort.

Since an improvement in the skeletal muscle effects of the agent (ie, an increase or decrease in muscle tone and reduced fasciculations) may be seen after oxime administration, medical personnel may be tempted to repeat the oxime along with atropine. Because of side effects, however, no more than about 2.5 g of oxime should be given within 1 to 1.5 hours. If the oxime is effective, it can be repeated once or twice at intervals of 60 to 90 minutes.

2-PAM Cl can be administered intravenously, intramuscularly, and orally. Soon after it became commercially available, 2-PAM Cl was administered orally both as therapy and as a pretreatment for those in constant contact with organophosphorus compounds (eg, crop dusters). At one time, the United Kingdom provided its military personnel with a supply of oxime tablets for pretreatment use, but it no longer does so. Enthusiasm for this practice waned for a number of reasons:

- erratic absorption of the drug from the gastrointestinal tract, leading to large differences (both between individuals and in the same person at different times) in plasma concentration;
- the large dose required (5 g to produce an average plasma concentration of 4 μg/mL);
- the unpopularity of the large, bitter 0.5-g or 1.0-g tablets; and
- the relatively slow absorption compared with that for administration by other routes.

In addition, the frequent administration (every 4–6 h) required by workers at risk caused gastrointestinal irritation, including diarrhea. It is also no longer common practice for crop workers to be given 2-PAM Cl as a pretreatment, the rationale being that crop workers who take the medication might have a false sense of security and therefore might tend to be careless with safety measures.

Despite these drawbacks, 2-PAM Cl tablets might be the best alternative in certain cases, such as a depot worker exposed to a nerve agent who shows no effects except for an inhibition of RBC-ChE activity. An oxime might be given to restore his RBC-ChE activity to 80% of his baseline value, which is necessary for his return to work. (See Blood Cholinesterases section, above, for discussion of monitoring RBC-ChE activity.) Administration by the oral route might be considered preferable (although less reliable) to administration by a parenteral route because tablets can be self-administered and taking tablets avoids the pain of an injection.

Intramuscular administration of 2-PAM Cl with the ComboPen results in a plasma concentration of 4 μg/kg at 7 minutes versus 10 minutes for con-

ventional needle-and-syringe injection.[130] (A maximal plasma concentration of 6.9 μg/kg occurs at 19 min vs 6.5 μg/kg at 22 min for the needle-and-syringe method.) About 80% to 90% of the intact drug is excreted unmetabolized in the urine; the half-life is about 90 minutes. When a 30% solution of 2-PAM Cl was injected intramuscularly at doses ranging from 2.5 to 30 mg/kg, the drug caused no change in heart rate or any signs or symptoms (except for pain at the injection site, as expected after an injection of 2 mL of a hypertonic solution).[146,147] When given intramuscularly, 30 mg/kg caused an elevation in blood pressure and minimal ECG changes, but no change in heart rate.[146]

Because of the very rapid aging of the soman–AChE complex, oximes are often considered ineffective in treating soman poisoning. Experimental studies in animals have shown that oximes are not nearly as effective in treating soman intoxication as in sarin intoxication, but they do provide some therapeutic benefit (a 5%–10% reactivation of the inhibited enzyme).[157,158] Suggested reasons for this benefit are that an oxime acts as a cholinergic blocking drug at the nicotinic sites, analogous to atropine at the muscarinic sites[157] or that it causes the circulation to improve, possibly by stimulating the release of catecholamines.[158]

Anticonvulsive Therapy

Convulsions occur after severe nerve agent exposure. In reports[18,63,81] of severe cases, convulsions (or what were described as "convulsive jerks" or "spasms") started within seconds after the casualty collapsed and lost consciousness, and persisted for several minutes until the individual became apneic and flaccid. The convulsions did not recur after atropine and oxime therapy and ventilatory support were administered. In these instances, no specific anticonvulsive therapy was needed nor was it given.

Laboratory studies indicate that the convulsive period lasts much longer (hours) in animals, even those given therapy. However, the antidotes are given in a standard dose to experimental animals rather than titrated to a therapeutic effect as they are in human patients; this difference may account for the greater duration of convulsions in animals. In animals, convulsions occur more frequently and are more severe when the animal is pretreated with pyridostigmine and given nerve agent followed by standard therapy than when no pyridostigmine pretreatment is used. For these reasons, it is anticipated that humans pretreated with pyridostigmine would also have more frequent and more severe convulsions when pretreated with pyridostigmine than when not pretreated with pyridostigmine.

Diazepam has been used successfully to terminate convulsions caused by organophosphate insecticide poisoning (see discussion of behavioral effects above) and has been fielded in the U.S. military. As discussed earlier, each soldier is issued one autoinjector (ComboPen) containing 10 mg of diazepam in 2 mL of diluent. When a soldier exposed to a nerve agent is unable to help himself, a buddy should administer diazepam as well as the contents of three MARK I kits—whether or not there are indications of seizure activity. In fact, it is preferable to administer diazepam before the onset of seizure activity. The medic carries additional diazepam injectors and is authorized to administer two additional injectors to a convulsing casualty at 10-minute intervals. Current military doctrine is for the buddy to administer the diazepam immediately following the administration of the third MARK I when the three MARK I kits are given together. This is not only military doctrine, it is sound medical advice, and this action should be taken automatically when assisting a casualty with severe exposure to organophosphate nerve agents.

Therapy for Cardiac Arrhythmias

Transient arrhythmias occur after nerve agent intoxication and after atropine administration in a normal individual. However, the irregularities generally terminate after the onset of atropine-induced sinus tachycardia (see discussion of cardiac effects, above).

Experimental studies[117,159] have shown that when animals are poisoned with ChE inhibitors and then allowed to become cyanotic, rapid intravenous administration of atropine will cause ventricular fibrillation. Ventricular fibrillation after rapid intravenous administration of atropine has not been reported in humans.

After severe intoxication from exposure to an organophosphate insecticide, a 20-year-old patient was stabilized with atropine and ventilatory support, but her ECG showed depression of the ST segment and flattening of the T wave, presumably because of persistent sinus tachycardia secondary to large doses of atropine (287 mg in 4 days; total of 830 mg). She was given a β-adrenergic blocking agent (propranolol), which slowed the heart rate to 107 beats per minute, normalizing the ST-T changes.

The normal ECG pattern and heart rate of 107 beats per minute persisted despite repeated doses of atropine. In effect, a pharmacologically isolated heart (with both cholinergic and adrenergic blockade) was produced; the authors reporting on the case suggested that propranolol might be of value in protecting against the effects of atropine and organophosphorus intoxication.[160]

SPECIFIC TREATMENT BY EXPOSURE CATEGORY

The goals of medical therapy are, in most cases, fairly straightforward: to minimize the patient's discomfort, to relieve distress, and to stop or reverse the abnormal process. These goals are the same in the treatment of a patient with nerve agent intoxication.

If a patient has severe dyspnea or vomiting (or retching), he or she may be unable to vocalize, but it can be assumed that the discomfort is severe. Therapy should be titrated against the complaints of dyspnea and objective manifestations such as retching; administration of the contents of MARK I kits (or atropine alone) should be continued at intervals until relief is obtained. Seldom are more than two to three MARK I kits required to provide relief. Because eye or head pain is not relieved by MARK I injections, a patient with severe eye or head pain from miosis will complain when he has no other injury that causes more overwhelming discomfort. Topical application of atropine or homatropine is quite effective in relieving this severe pain.

The signs of severe distress in a fellow soldier, such as twitching, convulsions, gasping for breath, and apnea, can be recognized by even a relatively untrained observer. A casualty's buddy will usually act appropriately, but because a buddy's resources are few, the level of assistance is limited: a buddy can administer three MARK I kits and diazepam and then seek medical assistance. In a more sophisticated setting, adequate ventilation is the highest priority, but even the best ventilators help little in the presence of copious secretions and high resistance in the airways. Atropine must be given until secretions (nose, mouth, airways) are decreased and resistance to assisted ventilation is minimal.

The goals of therapy must be realistic. Current drugs will not immediately restore consciousness or respiration or completely reverse the skeletal muscle abnormalities, nor will intramuscular or intravenous drug therapy reverse miosis. Muscular fasciculations and small amounts of twitching may continue in a conscious patient long after adequate ventilation is restored and the patient is walking and talking.

Although in practice exposure categories are never clear-cut, different therapeutic measures are recommended for treating nerve agent casualties who have different degrees of exposure severity. Treatment is based on the signs and symptoms caused by the particular exposure (Table 5-7). The following suggested exposure categories are based on the casualty's presenting signs and symptoms.

Suspected Exposure

Suspected, but unconfirmed, exposure to a nerve agent sometimes occurs in an area where liquid agent was present. A person without signs or symptoms may be unsure whether he is contaminated. In such cases, the suspected casualty should be thoroughly and completely decontaminated and kept under close medical observation for 18 hours. If a laboratory facility is available, blood should be drawn for measurement of RBC-ChE activity.

An individual working with nerve agent in an industrial or laboratory environment will have a baseline RBC-ChE activity value on record. If this value is still at baseline after a possible exposure, then no significant absorption has occurred, and the new value provides confirmation of the baseline. (See Blood Cholinesterases section, above, on RBC-ChE activity monitoring.) If the activity is decreased, however, then absorption of the agent has occurred, but the decision to begin therapy should be based on signs or symptoms, not on the RBC-ChE activity (with one possible exception: an asymptomatic worker with decreased ChE activity; see Oxime Therapy section, above). The medical care provider must remember that the nadir of RBC-ChE activity may not occur for 18 to 24 hours, and if there has been no oxime therapy, then the final sample for analysis must be drawn during that time period.

Since the onset of effects caused by nerve agent exposure may occur as long as 18 hours after skin contact, prolonged observation is prudent. The longer the interval until the onset of signs and symptoms, the less severe they will be, but medical assistance will still be necessary. Since vapor (or inhaled aerosol) causes effects within seconds or minutes, it is extremely unlikely that a "suspected" asymptomatic casualty would be produced by this route.

TABLE 5-7

RECOMMENDED THERAPY FOR CASUALTIES OF NERVE AGENTS

Exposure Route	Exposure Category	Signs and Symptoms	Therapy
Inhalational (Vapor)	Minimal	Miosis with or without rhinorrhea; reflex nausea and vomiting	< 5 min of exposure: 1 MARK I kit > 5 min of exposure*: observation
	Mild	Miosis; rhinorrhea; mild dyspnea; reflex nausea and vomiting	< 5 min of exposure: 2 MARK I kits > 5 min of exposure: 0 or 1 MARK I kit, depending on severity of dyspnea
	Moderate	Miosis; rhinorrhea; moderate to severe dyspnea; reflex nausea and vomiting	< 5 min of exposure: 3 MARK I kits + diazepam > 5 min of exposure: 1–2 MARK I kits
	Moderately severe	Severe dyspnea; gastrointestinal or neuromuscular signs	3 MARK I kits; standby ventilatory support; diazepam
	Severe	Loss of consciousness; convulsions; flaccid paralysis; apnea	3 MARK I kits; ventilatory support, suction; diazepam
Dermal (Liquid on Skin)	Mild	Localized sweating, fasciculations	1 MARK I kit
	Moderate	Gastrointestinal signs and symptoms	1 MARK I kit
	Moderately severe	Gastrointestinal signs plus respiratory or neuromuscular signs	3 MARK I kits; standby ventilatory support
	Severe	Same as for severe vapor exposure	3 MARK I kits; ventilatory support, suction; diazepam

*Casualty has been out of contaminated environment during this time.

Minimal Exposure

Miosis, with accompanying eye symptoms, and rhinorrhea are signs of a minimal exposure to a nerve agent, either vapor or vapor and liquid. This distinction is quite important in the management of this casualty. There are many situations in which one can be reasonably certain that exposure was by vapor alone (if the casualty was standing downwind from a munition or container, for example, or standing across a laboratory or storeroom from a spilled agent or leaking container). On the other hand, if an unprotected individual is close to an agent splash or is walking in areas where liquid agent is present, exposure may be by both routes. Effects from vapor exposure occur quickly and are at their maximum within minutes, whereas effects from liquid agent on the skin may not occur until hours later.

Atropine (and oxime) should not be given for miosis because it is ineffective in the usual doses (2 or 4 mg). If eye pain (or head pain) is severe, topical atropine or homatropine should be given. However, the visual blurring caused by atropine versus the relatively small amount of visual impairment caused by miosis must be considered. If the rhinorrhea is severe and troublesome, atropine (the 2 mg contained in one MARK I kit) may give some relief.

If liquid exposure is suspected, the patient must be kept under observation, as noted above. If liquid exposure can be excluded, there is no reason for prolonged observation.

Mild Exposure

An individual with mild or moderate dyspnea and possibly with miosis, rhinorrhea, or both can be classified as having a mild exposure to nerve agent. The symptoms indicate that the casualty has been exposed to a nerve agent vapor and may or may not have been contaminated by a liquid agent.

If an exposed person in this category is seen within several minutes after exposure, he should

receive the contents of two MARK I kits immediately. If 5 to 10 minutes have passed since exposure, the contents of only one kit should be given immediately. If no improvement occurs within 5 minutes under either circumstance, the casualty should receive the contents of another MARK I kit. The contents of an additional kit may be given if the casualty's condition worsens 5 to 10 minutes later, but it is unlikely that it will be needed. Only three oxime autoinjectors should be given; further therapy should be with atropine alone.

A person having mild exposure to a nerve agent should be thoroughly decontaminated (exposure to vapor alone does not require decontamination) and have blood drawn for measurement of RBC-AChE activity prior to MARK I administration if facilities are available for the assay. As noted above, if there is reason to suspect liquid exposure, the casualty should be observed longer.

Moderate Exposure

A casualty who has had moderate exposure to either a nerve agent vapor alone or to vapor and liquid will have severe dyspnea, with accompanying physical signs, and probably also miosis and rhinorrhea. The casualty should be thoroughly decontaminated (REMEMBER: exposure to vapor alone does not require decontamination) and blood should be drawn for assay of RBC-ChE activity if assay facilities are available. The contents of three MARK I kits and diazepam should be given if the casualty is seen within minutes of exposure. If seen later than 10 minutes after exposure, the casualty should receive the contents of two kits. Additional atropine should be given at 5- to 10-minute intervals until the dyspnea subsides. No more than three MARK I kits should be used; however, additional atropine alone should be administered if the contents of three kits do not relieve the dyspnea after 10 to 15 minutes. If there is reason to suspect liquid contamination, the patient should be kept under observation for 18 hours.

Nausea and vomiting are frequently the first effects from liquid contamination; the sooner after exposure they appear, the more ominous the outlook. Therapy should be more aggressive when these symptoms occur within an hour after exposure than when there is a longer delay in onset. If the onset is about an hour or less from the known time of liquid exposure, the contents of two MARK I kits should be administered initially, and further therapy (the contents of MARK I kits to a total of three, then atropine alone) given at 5- to 10-minute intervals, with a maximum of three oxime injections. If the onset is several hours after the time of known exposure, the contents of one MARK I kit should be given initially, and additional MARK I kits as needed to a total of three. Atropine alone should be used after the third MARK I. If the time of exposure is unknown, the contents of two MARK I kits should be administered.

Nausea and vomiting that occur several hours after exposure have been treated successfully with 2 or 4 mg of atropine, and the symptoms did not recur. However, the exposure was single-site exposure (one drop at one place). It is not certain that this treatment will be successful if exposure is from a splash or from environmental contamination with multiple sites of exposure on the skin. Therefore, casualties with this degree of exposure should be observed closely for at least 18 hours after the onset of signs and symptoms.

Moderately Severe Exposure

In cases of moderately severe exposure, the casualty will be conscious and have one or more of the following signs and symptoms: severe respiratory distress (marked dyspnea and objective signs of pulmonary impairment such as wheezes and rales), marked secretions from the mouth and nose, nausea and vomiting (or retching), and muscular fasciculations and twitches. Miosis may be present if exposure was by vapor, but it is a relatively insignificant sign as a guideline for therapy in this context.

The contents of three MARK I kits should be administered immediately. Preferably, if the means are available, 2 or 4 mg of atropine should be given intravenously, and the remainder of the total amount of 6 mg of atropine, along with the three oxime injections, should be given intramuscularly. The anticonvulsant diazepam should always be given when the contents of three MARK I kits are administered together. The casualty should be thoroughly decontaminated and have blood drawn for AChE assay before oxime is given.

Again, knowledge of the route of exposure is useful in planning further treatment. If the exposure was by vapor only and the casualty is seen in a vapor-free environment some minutes later, drug therapy should result in improvement. If the casualty has not lost consciousness, has not convulsed, and has not become apneic, he should improve. If the exposure was the result of liquid agent or a combination of liquid and vapor, there may be a reservoir of unabsorbed agent in the skin; despite the

initial therapy, the casualty's condition may worsen. In either case, medical care providers should be prepared to provide ventilatory assistance, including adequate suction, and additional drug therapy (atropine alone) if there is no improvement within 5 minutes after intravenous administration of atropine, or 5 to 10 minutes after intramuscular administration of atropine.

The triad of consciousness, lack of convulsive activity, and spontaneous respiration is an indicator of a good outcome, provided adequate therapy is given early.

Severe Exposure

A casualty who is severely exposed to a nerve agent will be unconscious. He may be apneic or gasping for air with marked cyanosis, and may be convulsing or postictal. The casualty will have copious secretions from the mouth and nose and will have generalized fasciculations in addition to convulsive or large-muscle twitching movements. If the casualty is postictal, he may be flaccid and apneic.

If the casualty shows no movement, including no signs of respiration, the initial response should be to determine if the heart is beating. This is not an easy task when the rescuer and the casualty are both in full mission-oriented protective posture (MOPP 4) gear, but it must be accomplished because a nonmoving, nonbreathing casualty without a heartbeat is not a candidate for further attention on the battlefield. In a medical treatment facility, the medical personnel may be slightly more optimistic and proceed with aggressive therapy. After the sarin release in the Tokyo, Japan, subways, several casualties who were not breathing and who had no cardiac activity were taken to a hospital emergency department. Because of very vigorous and aggressive medical management, one or two of these casualties were able to walk out of the hospital several days later.

Despite the circumstances, self-protection from contamination from the patient is important. Since decontamination of the patient may not be the first priority, caregivers must wear appropriate protective equipment until they have an opportunity to decontaminate the casualty and to remove him and themselves from the contaminated area.

The success of therapy under these circumstances is directly proportional to the viability of the casualty's cardiovascular system. If the heart rate is very slow or nonexistent or if there is severe hypotension, the chances for success are poor, even in the best possible circumstances.

First, medical personnel must provide oxygenation and administer atropine by a technique that ensures it will be carried to the heart and lungs. If ventilatory assistance is not immediately available, the best treatment is to administer the contents of three MARK I kits and diazepam. If ventilatory assistance will be forthcoming within minutes, the contents of the three MARK I kits should be administered whether the circulation is intact or not. When there is no chance of rapid ventilatory assistance, little is gained by MARK I therapy, but an attempt at treatment should be made anyway.

In the case of a failed or failing cardiovascular system, routes of atropine administration other than intramuscular should be considered. The intravenous route generally provides the fastest delivery of the drug throughout the body, but it is not without danger in an apneic and cyanotic patient. Whether or not concomitant ventilatory support can be provided, military medical personnel might want to consider administering atropine intratracheally by needle and syringe, if available, or with the atropine autoinjector (the AtroPen). Even if the casualty's systemic blood pressure is low, the peribronchial circulation may still have adequate blood flow to carry the drug to vital areas. If an endotracheal tube can be inserted, atropine could be injected into the tube either by needle and syringe or with the injector.

For severely exposed casualties, the initial dose of atropine should be at least the 6 mg from the three autoinjectors, but an additional 2 mg or 4 mg should also be given intravenously—if the capability is available and if the casualty is not hypoxic (ventilatory support must be started before intravenous atropine is given). If additional atropine cannot be given intravenously, then the amount should be given intramuscularly. The total initial dose of atropine can be as much as 10 mg, but this dose should not be exceeded without allowing at least several minutes for a response. Further atropine administration depends on the response. If secretions decrease or if there are attempts at breathing, it might be prudent to wait even longer before administering additional atropine. All three injectors of 2-PAM Cl should be given with the initial 6 mg of atropine, but no more oxime should be given for an hour.

Possibly the most critical factor in treatment of severely exposed casualties is restoration of oxygenation. Atropine alone might restore spontaneous breathing in a small number of apneic individuals. Ideally, an apparatus that delivers oxygen under positive pressure will be available. Even an RDIC or a mask-valve-bag apparatus used with ambient air will provide some assistance.

When the contents of three MARK I kits are administered together to a severely poisoned casualty, diazepam should be administered with the contents of the third MARK I—whether or not there are indications of seizure activity. The risk of respiratory depression from this amount of diazepam given intramuscularly is negligible.

Hypotension per se need not be treated, at least initially. Generally the restoration of oxygenation and the increase in heart rate caused by atropine, aided perhaps by the hypertensive effects of 2-PAM Cl, will cause the blood pressure to increase to an acceptable level.

Even with adequate oxygenation and large amounts of atropine, immediate reversal of all of the effects of the nerve agent will not occur. The casualty may remain unconscious, without spontaneous respiration and with muscular flaccidity or twitching, for hours. Even after respiration is at least partly spontaneous, secretions are minimized, and the casualty is partly alert, close monitoring is necessary. Muscular fasciculations may continue for hours after the casualty is alert enough and has strength enough to get out of bed.

RETURN TO DUTY

Various factors should be considered before an individual who has been a nerve agent casualty is returned to duty. In an industrial setting (depot or laboratory), the criteria for reactivation are that the individual's RBC-ChE activity must have returned to within 80% of its baseline value and that the individual is otherwise symptom- and sign-free.

In a military field setting, however, ChE-activity measurements are not available, and the need to return the fighting soldier to duty may be more acute. The decision is largely a matter of judgment and should include the following considerations:

- If exposed to nerve agent again, will the soldier be in greater danger because of the previous exposure?
- How well can the soldier function?
- What is the military need for the soldier?

In the absence of blood ChE measurements, it is difficult to predict whether a soldier would be at greater risk from a second nerve agent exposure. Even an individual with rather mild effects (miosis and rhinorrhea) may have marked ChE inhibition. On the other hand, if an oxime (contained in the MARK I kit) was given and the agent was one susceptible to oxime therapy, then the enzyme activity may be restored. In a field setting, neither the identity of the agent nor the degree of ChE inhibition or restoration will be known. In any case, proper use of MOPP 4 gear should protect against further exposure. If the soldier is able and needed, he should be returned to duty.

A soldier who has had signs of severe exposure, with loss of consciousness, apnea, and convulsions, may have milder CNS effects for many weeks after recovery from the acute phase of intoxication. Except in dire circumstances, return to duty during this period should not be considered for such casualties.

An individual with relatively mild effects (miosis, dyspnea, rhinorrhea) may be returned to duty within 1 to several days or even hours, depending on the assignment and the military need. However, the soldier may experience visual problems in dim light and may have mental lapses for as long as 6 to 8 weeks[18] (and personal observation); these factors must be considered before returning a soldier to duty. Several observations support this conclusion. In one case, troops who were symptomatic (miosis, rhinorrhea, dyspnea) as a result of nerve agent exposure carried out maneuvers (including firing weapons) in a satisfactory, although suboptimal, manner. They did not do nearly as well at night because of visual problems.[79]

In another instance, workers in an industrial operation learned the effects of the agent after they had accidentally been exposed several times. They also learned that it was a bigger problem to seek medical aid (with the ensuing administrative processes) than to continue working in the presence of symptoms. They stopped going to the aid station if they noted the onset of only mild effects. These workers were generally not in positions requiring acute vision or complex decisions; it is not known how well they performed while symptomatic. However, they could continue to perform their jobs, and their supervisors apparently did not notice a decrement (personal observation).

The need for soldiers in a frontline military operation may require that every walking casualty be returned to duty. In an otherwise asymptomatic casualty, the primary limiting factors will be (1) the soldier's visual acuity compared with the visual demands of the job and (2) the soldier's mental status compared with the intellectual demands of the job. Prolonged mental changes can be subtle and may require a careful examination to detect.

SUMMARY

Nerve agents are the most toxic chemical warfare agents known. They cause effects within seconds and death within minutes. These agents are in the military stockpiles of several countries but have been used in only one war. They can be manufactured by terrorist groups and have been used in terrorist attacks.

Nerve agents cause biological effects by inhibiting the enzyme AChE, causing an excess of the neurotransmitter to accumulate. Hyperactivity in those organs innervated by cholinergic nerves results, with increased secretions from exocrine glands, hyperactivity of skeletal muscles leading to fatigue and paralysis, hyperactivity of smooth muscles with bronchoconstriction, and CNS changes, including seizure activity and apnea.

Therapy is based on the administration of atropine, which interferes with receptor binding of acetylcholine at muscarinic but not nicotinic receptors, and the oxime 2-PAM Cl, which breaks the agent–enzyme bond formed by most agents. Assisted ventilation and other supportive measures are also required in severe poisoning.

REFERENCES

1. Koelle GB. Anticholinesterase agents. In: Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics*. 5th ed. New York, NY: Macmillan; 1975: 445.

2. Davis W. *The Serpent and the Rainbow*. New York: Warner Books Inc; 1985: 36–37.

3. Fraser TR. On the characters, actions, and therapeutic use of the ordeal bean of Calabar. *Edinb Med J.* 1863;9:124–132.

4. Holmstedt B. Structure–activity relationships of the organophosphorus anticholinesterase agents. In: Koelle GB, ed. *Cholinesterases and Anticholinesterase Agents*. Berlin, Germany: Springer Verlag; 1963: 429.

5. Harris R, Paxman J. *A Higher Form of Killing*. New York, NY: Hill and Wang; 1982: 53.

6. Robinson JP. *The Rise of CB Weapons*. Vol 1. In: *The Problem of Chemical and Biological Warfare.* New York, NY: Humanities Press; 1971: 71.

7. Kenneth W. Wilson, Directorate of Medical Research, Edgewood Arsenal, Md. Personal communications, mid to late 1960s.

8. Wills JH, DeArmon IA. *A Statistical Study of the Adamek Report*. Army Chemical Center, Md: Medical Laboratories; 1954. Medical Laboratory Special Report 54.

9. Program Executive Officer—Program Manager for Chemical Demilitarization. *Chemical Stockpile Disposal Program: Final Programmatic Environmental Impact Statement*. Aberdeen Proving Ground, Md: Program Manager for Chemical Demilitarization; Jan 1988. Publication A3, vol 3.

10. Smith RJ. Army poison gas stockpile raises worries in Kentucky. *Washington Post.* 1989;Jan 22:1, 9.

11. Koelle GB. Anticholinesterase agents. In: Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics*. 4th ed. New York, NY: Macmillan; 1970: 446.

12. O'Neill JJ. Non-cholinesterase effects of anticholinesterases. *Fundam Appl Toxicol.* 1981;1:154–160.

13. Albuquerque A, Alaike APS, Rickett DL. The interaction of anticholinesterase agents with acetylcholine receptor–ionic channel complex. *Fundam Appl Toxicol.* 1984;4:527–533.

14. Koelle GB. Protection of cholinesterase against irreversible inactivation by di-isopropyl fluorophosphate in vitro. *J Pharmacol Exp Ther.* 1946;88:232–237.

15. Koster R. Synergisms and antagonisms between physostigmine and di-isopropyl fluorophosphate in cats. *J Pharmacol Exp Ther.* 1946;88:39–46.

16. Freedman AM, Willis A, Himwich HE. Correlation between signs of toxicity and cholinesterase level of brain and blood during recovery from di-isopropyl fluorophosphate (DFP) poisoning. *Am J Physiol.* 1948;157:80–87.

17. Oberst FW, Christensen MK. Regeneration of erythrocyte and brain cholinesterase activity in rats after sublethal exposures to GB vapor. *J Pharmacol Exp Ther.* 1956;116:216–219.

18. Sidell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol.* 1974;7:1–17.

19. Evans ES Jr, Olds KL, Weyandt TB. Pesticides. In: Deeter DP, Gaydos JC, eds. *Occupational Health: The Soldier and the Industrial Base.* In: Zajtchuk R, Bellamy RF, eds. *Textbook of Military Medicine*. Washington, DC: US Department of the Army, Office of The Surgeon General, and Borden Institute; 1993: 532–536.

20. Hayes WJ. Organic phosphorus pesticides. In: Hayes WJ, ed. *Pesticides Studied in Man*. Baltimore, Md: Williams & Wilkins; 1982: 284–435.

21. Adler M, Filbert MG. Role of butyrylcholinesterase in canine tracheal smooth muscle function. *FEBS Lett*. 1990;267:107–110.

22. Kent KM, Epstein SE, Cooper T, Jacobowitz DM. Cholinergic innervation of the canine and human ventricular conducting system. *Circulation.* 1974:50:948–955.

23. Slavkov J, Vik J, Hlavickov V. Acetylcholinesterase and butyrylcholinesterase activity in the atria of the heart of adult albino rats. *Physiol Bohemoslov.* 1982;31:407–414.

24. Kalow W, Genest K. A method for the detection of atypical forms of human serum cholinesterase: Determination of dibucaine numbers. *Can J Biochem Physiol.* 1957;35:339–346.

25. Neitlich H. Increased plasma cholinesterase activity and succinylcholine resistance: A genetic variant. *J Clin Invest.* 1966;45:380–386.

26. Johns RJ. Familial reduction in red cell cholinesterase. *N Engl J Med.* 1962;267:1344–1348.

27. Wetstone HJ, LaMotta RV. The clinical stability of serum cholinesterase activity. *Clin Chem.* 1965;11:653–663.

28. Sidell FR, Kaminskis A. Temporal intrapersonal physiological variability of cholinesterase activity in human plasma and erythrocytes. *Clin Chem.* 1975;21:1961–1963.

29. Shanor SP, van Hees GR, Baart N, Erdos EEG, Foldes FF. The influence of age and sex on human plasma and red cell cholinesterase. *Am J Med Sci.* 1961;242:357–361.

30. Sidell FR, Kaminskis A. Influence of age, sex, and oral contraceptives on human blood cholinesterase activity. *Clin Chem.* 1975;21:1393–1395.

31. Robertson GS. Serum protein and cholinesterase changes in association with contraceptive pills. *Lancet.* 1967;i:232–235.

32. Whittaker M. Charlier AR, Ramaswamy S. Changes in plasma cholinesterase isoenzyme due to oral contraceptives. *J Reprod Fertil.* 1971;26:373–375.

33. Callaway S, Davies DR, Rutland JP. Blood cholinesterase levels and range of personal variation in a healthy adult population. *Br Med J.* 1951;ii:812–816.

34. Augustinsson K. The normal variation of human blood cholinesterase activity. *Acta Physiol Scand.* 1955;35:40–52.

35. Ketchum JS, Sidell FR, Crowell EB Jr, Aghajanian GK, Hayes AH Jr. Atropine, scopolamine, and Ditran: Comparative pharmacology and antagonists in man. *Psychopharmacology (Berlin).* 1973;28:121–145.

36. Grob D, Lilienthal JL Jr, Harvey AM, Jones BF. The administration of di-isopropyl fluorophosphate (DFP) to man, I: Effect on plasma and erythrocyte cholinesterase; general systemic effects; use in study of hepatic function and erythropoieses; and some properties of plasma cholinesterase. *Bull Johns Hopkins Hosp.* 1947;81:217–244.

37. Rider JA, Moeller HC, Puletti EJ, Swader JI. Toxicity of parathion, systox, octamethyl pyrophosphoramide, and methyl parathion in man. *Toxicol Appl Pharmacol.* 1969;14:603–611.

38. Hayes GR, Funckes AJ, Hartwell WV. Dermal exposure of human volunteers to parathion. *Arch Environ Health.* 1964;8:829–833.

39. Edson EF. No-effect levels of three organophosphates in the rat, pig, and man. *Food Cosmet Toxicol.* 1964;2:311–316.

40. Rider JA, Puletti EJ, Swader JI. The minimal oral toxicity level for mevinphos in man. *Toxicol Appl Pharmacol.* 1975;32:97–100.

41. Sidell FR, Groff WA. The reactivatibility of cholinesterase inhibited by VX and sarin in man. *Toxicol Appl Pharmacol.* 1974;27:241–252.

42. Sim VM. *Variability of Different Intact Human Skin Sites to the penetration of VX*. Edgewood Arsenal, Md: Medical Research Laboratory; 1962. Chemical Research and Development Laboratory Report 3122.

43. Grob D, Harvey JC. Effects in man of the anticholinesterase compound sarin (isopropyl methyl phosphonofluoridate). *J Clin Invest.* 1958;37:350–368.

44. Grob D, Harvey AM. The effects and treatment of nerve gas poisoning. *Am J Med.* 1953;14:52–63.

45. Sim VM, Stubbs JL. *VX Percutaneous Studies in Man*. Edgewood Arsenal, Md: Medical Research Laboratory; 1960. Chemical Research and Development Laboratory Report 3015.

46. Craig FN, Cummings EG, Sim VM. Environmental temperature and the percutaneous absorption of a cholinesterase inhibitor, VX. *J Invest Dermatol.* 1977;68:357–361.

47. Ministry of Defence. *Cholinesterase as an Aid in the Early Diagnosis of Nerve Gas Poisoning. Part II: The Variation of Blood Cholinesterase in Man Before and After the Administration of Very Small Quantities of G Vapor by Inhalation*. United Kingdom: Ministry of Defence. Unpublished report, n.d.

48. Harvey JC. *Clinical Observations on Volunteers Exposed to Concentrations of GB*. Edgewood Arsenal, Md: Medical Research Laboratory; 1952. Medical Laboratory Research Report 144.

49. Craig AB, Woodson GS. Observations on the effects of exposure to nerve gas, I: Clinical observations and cholinesterase depression. *Am J Med Sci.* 1959;238:13–17.

50. Sidell RF. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. New York, NY: Academic Press; 1992: 163.

51. Namba T, Nolte CT, Jackrel J, Grob D. Poisoning due to organophosphate insecticides. *Am J Med.* 1971;59:475–492.

52. Johns RJ. *The Effects of Low Concentrations of GB on the Human Eye*. Edgewood Arsenal, Md: Medical Research Laboratory; 1952. Medical Laboratory Research Report 100.

53. Rengstorff RH. Accidental exposure to sarin: Vision effects. *Arch Toxicol.* 1985;56:201–203.

54. Stewart WC, Madill HD, Dyer AM. Night vision in the miotic eye. *Can Med Assoc J.* 1968;99:1145–1148.

55. Craig AB Jr, Freeman G. *Clinical Observations on Workers Accidentally Exposed to "G" Agents*. Edgewood Arsenal, Md: Medical Research Laboratory; 1953. Medical Laboratory Research Report 154.

56. Rubin LS, Krop S, Goldberg MN. Effect of sarin on dark adaptation in man: Mechanism of action. *J Appl Physiol.* 1957;11:445–449.

57. Rubin LS, Goldberg MN. Effect of tertiary and quaternary atropine salts on absolute scotopic threshold changes produced by an anticholinesterase (sarin). *J Appl Physiol.* 1958;12:305–310.

58. Trussov MS. Effects of eserine upon light sensitivity and dark adaption. *Oftalmol J Ukraine.* 1962;17:366–371.

59. Moylan-Jones RJ, Thomas DP. Cyclopentolate in treatment of sarin miosis. *Br J Pharmacol.* 1973;48:309–313.

60. Ministry of Defence. *An Evaluation of the Functional Changes Produced by the Inhalation of GB Vapour*. United Kingdom: Ministry of Defence. Unpublished report, n.d.

61. Ministry of Defence. *Air-Way Resistance Changes in Men Exposed to GB Vapour*. United Kingdom: Ministry of Defence. Unpublished report, n.d.

62. Clements JA, Moore JC, Johnson RP, Lynott J. *Observations on Airway Resistance in Men Given Low Doses of GB by Chamber Exposure*. Edgewood Arsenal, Md: Medical Research Laboratory; 1952. Medical Laboratory Research Report 122.

63. Ward JR. Case report: Exposure to a nerve gas. In: Whittenberger JL, ed. *Artificial Respiration: Theory and Applications*. New York, NY: Harper & Row; 1962: 258–265.

64. De Candole CA, Douglas WW, Evans CL, et al. The failure of respiration in death by anticholinesterase poisoning. *Br J Pharmacol Chemother.* 1953;8:466–475.

65. Ministry of Defence. *The Predominantly Peripheral Effects of Acute GB Poisoning in Anaesthetised Animals*. United Kingdom: Ministry of Defence. Unpublished report, n.d.

66. Johnson RP, Gold AJ, Freeman G. Comparative lung-airway resistance and cardiovascular effects in dogs and monkeys following parathion and sarin intoxication. *Am J Physiol.* 1958;192:581–584.

67. Fredriksson T, Hansson C, Holmstedt B. Effects of sarin in the anaesthetized and unanaesthetized dog following inhalation, percutaneous absorption and intravenous infusion. *Arch Int Pharmacodyn Ther.* 1960;126:288–302.

68. Wright PG. An analysis of the central and peripheral components of respiratory failure produced by anticholinesterase poisoning in the rabbit. *J Physiol (Lond).* 1954;126:52–70.

69. Rickett DL, Glenn JF, Beers ET. Central respiratory effects versus neuromuscular actions of nerve agents. *Neurotoxicology.* 1986;7:225–236.

70. Kluwe WM, Chinn JC, Feder P, Olson C, Joiner R. Efficacy of pyridostigmine pretreatment against acute soman intoxication in a primate model. In: *Proceedings of the Sixth Medical Chemical Defense Bioscience Review.* Aberdeen Proving Ground, Md: US Army Medical Research Institute for Chemical Defense; 1987: 227–234. Report AD B121516.

71. Firemark H, Barlow CF, Roth LC. The penetration of 2-PAM-Cl^{14} into brain and the effects of cholinesterase inhibitors on its transport. *J Pharmacol Exp Ther.* 1964;145:252–265.

72. Brown EC Jr. *Effects of G Agents on Man: Clinical Observations*. Edgewood Arsenal, Md: Medical Laboratory; 1948. Medical Division Report 158.

73. Craig AB Jr, Cornblath M. *Further Clinical Observations in Workers Accidentally Exposed to G Agents*. Edgewood Arsenal, Md: Medical Research Laboratory; 1953. Medical Laboratory Research Report 234.

74. Brody BB, Gammill JF. *Seventy-Five Cases of Accidental Nerve Gas Poisoning at Dugway Proving Ground*. Dugway Proving Ground, Utah: Medical Investigational Branch; 1954. Medical Investigational Branch Special Report 5.

75. Bowers MB, Goodman E, Sim VN. Some behavioral changes in man following anticholinesterase administration. *J Nerv Ment Dis.* 1964;138:383–389.

76. Ministry of Defence. *Psychological Effects of a G-Agent on Men.* United Kingdom: Ministry of Defence. Unpublished report, n.d.

77. Ministry of Defence. *Psychological Effects of a G-Agent on Men: 2nd Report*. United Kingdom: Ministry of Defence. Unpublished report, n.d.

78. Ministry of Defence. *The Effects of a Single Exposure to GB (Sarin) on Human Physical Performance*. United Kingdom: Ministry of Defence. Unpublished report, n.d.

79. Ministry of Defence. *The Effects of a Minor Exposure to GB on Military Efficiency*. United Kingdom: Ministry of Defence. Unpublished report, n.d.

80. Grob D, Harvey AM, Langworthy OR, Lilienthal JL Jr. The administration of di-isopropyl fluorophosphate (DFP) to man, III: Effect on the central nervous system with special reference to the electrical activity of the brain. *Bull Johns Hopkins Hosp.* 1947;81:257–266.

81. Grob D. The manifestations and treatment of poisoning due to nerve gas and other organic phosphate anticholinesterase compounds. *Arch Intern Med.* 1956;98:221–239.

82. Levin HS, Rodnitzky RL. Behavioral effects of organophosphate pesticides in man. *Clin Toxicol.* 1976;9:391–405.

83. Karczmar AG. Acute and long lasting central actions of organophosphorus agents. *Fundam Appl Toxicol.* 1984;4:S1–S17.

84. Duffy FH, Burchfiel JL, Bartels PH, Gaon M, Sim VM. Long-term effects of an organophosphate upon the human electroencephalogram. *Toxicol Appl Pharmacol.* 1979;47:161–176.

85. Lemercier G, Carpentier P, Sentenae-Roumanou H, Morelis R. Histological and histochemical changes in the central nervous system of the rat poisoned by an irreversible anticholinesterase organophosphorus compound. *Acta Neuropathol.* 1983;61:123–129.

86. Petras JM. Brain pathology induced by organophosphate poisoning with the nerve agent soman. In: *Proceedings of the Fourth Annual Chemical Defense Bioscience Review*. Aberdeen Proving Ground, Md: US Army Medical Research Institute for Chemical Defense; 1985: 407–414.

87. McLeod CG Jr, Singer AW, Harrington DG. Acute neuropathology in soman poisoned rats. *Neurotoxicology.* 1984;5:53–58.

88. Singer AW, Jaax NK, Graham JS, McLeod CG Jr. Cardiomyopathy in soman and sarin intoxicated rats. *Toxicol Lett.* 1987;36:243–249.

89. McDonough JH Jr, McLeod CG Jr, Nipwoda T. Direct microinjection of soman or VX into the amygdala produces repetitive limbic convulsions and neuropathology. *Brain Res.* 1987;435:123–137.

90. Raffaele K, Hughey D, Wenk G, Olton D, Modrow H, McDonough J. Long-term behavioral changes in rats following organophosphonate exposure. *Pharmacol Biochem Behav.* 1987;27:407–412.

91. McDonough JH Jr, Smith RF, Smith CD. Behavioral correlates of soman-induced neuropathology: Deficits in DRL acquisition. *Neurobehav Toxicol Teratol.* 1986;8:179–187.

92. Modrow HE, Jaax NK. Effect of soman exposure on the acquisition of an operant alternation task. *Pharmacol Biochem Behav.* 1989;32:49–53.

93. Blennow G, Brierley JB, Meldrum BS, Siesjo BK. Epileptic brain damage: The role of systemic factors that modify cerebral energy metabolism. *Brain*. 1978;101:687–700.

94. Soderfeldt B, Blennow G, Kalimo H, Olsson Y, Siesjo BK. Influence of systemic factors on experimental epileptic brain injury. *Acta Neuropathol.* 1983;60:81–91.

95. Wall HG. Brain lesions in rhesus monkeys after acute soman intoxication. In: *Proceedings of the Sixth Medical Chemical Defense Bioscience Review*. Aberdeen Proving Ground, Md: US Army Medical Research Institute for Chemical Defense; 1987: 155–162.

96. Lipp JA. Effect of benzodiazepine derivatives upon soman induced seizure activity and convulsions in the monkey. *Acta Int Pharmacodyn.* 1973;202:241–251.

97. Rump S, Grudzinska E, Edelwein Z. Effects of diazepam on abnormalities of bioelectrical activity of the rabbit's brain due to fluostigmine. *Act Nerv Super. 1972;*14:176–177.

98. Rump S, Grudzinska E, Edelwein Z. Effects of diazepam on epileptiform patterns of bioelectrical activity of the rabbit brain induced by fluostigmine. *Neuropharmacology.* 1973;12:815–819.

99. Martin LJ, Doebler JA, Shih T, Anthony A. Protective effect of diazepam pretreatment on soman-induced brain lesion formation. *Brain Res.* 1985;325:287–289.

100. McDonough JH Jr, Jaax NK, Crowley RA, Mays MZ, Modrow HE. Atropine and/or diazepam therapy protects against soman-induced neural and cardiac pathology. *Fundam Appl Toxicol.* 1989;13:256–276.

101. Hayward IJ, Wall HG, Jaax NK, Wade JV, Marlow DD, Nold JB. *Influence of Therapy With Anticonvulsant Compounds on the Effects of Acute Soman Intoxication in Rhesus Monkeys*. Aberdeen Proving Ground, Md: US Army Medical Research Institute for Chemical Defense; 1988. Technical Report 88-12.

102. *Proceedings of Workshop on Convulsions and Related Brain Damage Induced by Organophosphorus Agents*. Aberdeen Proving Ground, Md: US Army Medical Research Institute for Chemical Defense; 1990. USAMRICD-SP-90-02.

103. Meldrum BD. Metabolic factors during prolonged seizures and their relation to nerve cell death. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. *Advances in Neurology*. 34th ed. New York, NY: Raven Press; 1983: 261–275.

104. Nevander G, Ingvar M, Auer R, Siesjo BK. Status epilepticus in well-oxygenated rats causes neuronal necrosis. *Ann Neurol.* 1985;18:281–290.

105. Nevander G, Ingvar M, Auer R, Siesjo BK. Irreversible neuronal damage after short periods of status epilepticus. *Acta Physiol Scand.* 1984;120:155–157.

106. Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. *Arch Neurol.* 1973;28:10–17.

107. Soderfeldt B, Kalimo H, Olsson Y, Siesjo BK. Bicuculline-induced epileptic brain injury. *Acta Neuropathol.* 1983;62:87–95.

108. Orlowski JP, Erenberg G, Lueders H, Cruse RP. Hypothermia and barbiturate coma for refractory status epilepticus. *Crit Care Med.* 1984;12:367–372.

109. Aicardi J, Chevrie J. Consequences of status epilepticus in infants and children. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. *Advances in Neurology.* 34th ed. New York, NY: Raven Press; 1983: 115–124.

110. Oberst FW, Ross RS, Christensen MK, Crook JW, Cresthull P, Umland CW. Resuscitation of dogs poisoned by inhalation of the nerve gas GB. *Milit Med.* 1956;119:377–386.

111. Pazdernik TL, Cross RS, Giesler M, Samson FE, Nelson SR. Changes in local cerebral glucose utilization induced by convulsants. *Neuroscience.* 1985;14:823–835.

112. Kiss Z, Fazekas T. Arrhythmias in organophosphate poisoning. *Acta Cardiol.* 1979;5:323–330.

113. Hassler CR, Moutvic RR, Hamlin RL. Studies of the action of chemical agents on the heart. In: *Proceedings of the Sixth Medical Chemical Defense Bioscience Review*. Aberdeen Proving Ground, Md: US Army Medical Research Institute for Chemical Defense; 1987: 551–554.

114. Hassler CR, Moutvic RR, Hobson DW, et al. Long-term arrhythmia analysis of primates pretreated with pyridostigmine, challenged with soman, and treated with atropine and 2-PAM. In: *Proceedings of the 1989 Medical Chemical Defense Bioscience Review*. Aberdeen Proving Ground, Md: US Army Medical Research Institute for Chemical Defense; 1989: 479–482.

115. Ludomirsky A, Klein HO, Sarelli P, et al. Q-T prolongation and polymorphous ("torsade de pointes") ventricular arrhythmias associated with organophosphorus insecticide poisoning. *Am J Cardiol.* 1982;49:1654–1658.

116. Freeman G. Ludemann H, Cornblath M, et al. *Cardiovascular and Respiratory Effects of Acute Parathion Poisoning in Dogs with Particular Regard to Ventricular Fibrillation*. Army Chemical Center, Md: Medical Laboratories; 1954. Medical Laboratory Research Report 303.

117. Kunkel AM, O'Leary JF, Jones AH. *Atropine-Induced Ventricular Fibrillation During Cyanosis Caused by Organophosphorus Poisoning*. Edgewood Arsenal, Md: Medical Research Laboratory; 1973. Edgewood Arsenal Technical Report 4711.

118. Bellet S. *Clinical Disorders of the Heart Beat*. Philadelphia, Pa: Lea & Febiger; 1963: 110.

119. Ganendran A. Organophosphate insecticide poisoning and its management. *Anaesth Intensive Care.* 1974;2:361–368.

120. Willems J, Vermeire P, Rolly G. Some observations on severe human poisonings with organophosphate pesticides. *Arch Toxicol.* 1971;28:182–191.

121. van Hooidonk C, Ceulen BI, Bock J, van Genernen J. CW agents and the skin: Penetration and decontamination. In: *Proceedings of the International Symposium on Protection Against Chemical Warfare Agents*. Stockholm, Sweden: FOA Reports; 1983: 153–160.

122. Davies DR, Green AL, Willey GL. 2-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate and atropine in the treatment of severe organophosphate poisoning. *Br J Pharmacol.* 1959;14:5–8.

123. Sidell FR, Mershon MM, Savola RH, Schwartz HN, Wiles JS, McShane WP. *Treatment of Percutaneous VX Intoxication in Rabbits Under Conditions Simulating Self-Therapy in the Field*. Edgewood Arsenal, Md: Medical Research Laboratory; 1968. Technical Memorandum 114–22.

124. Ainsworth M, Shephard RJ. The intrabronchial distribution of soluble vapours at selected rates of gas flow. In: Davies CN, ed. *Inhaled Particles and Vapours*. New York, NY: Pergamon Press; 1961: 233–247.

125. Oberst FW. Factors affecting inhalation and retention of toxic vapors. In: Davies CN, ed. *Inhaled Particles and Vapours*. New York, NY: Pergamon Press; 1961: 249–265.

126. Oberst FW, Koon WS, Christensen MK, Crook JW, Cresthull P, Freeman G. Retention of inhaled sarin vapor and its effect on red blood cell cholinesterase activity in man. *Clin Pharmacol Ther.* 1968;9:421–427.

127. Fraser TR. An experimental research on the antagonism between the actions of physostigma and atropia. *Trans R Soc Edinb.* 1870;26:259–713.

128. Barrett, et al. Unpublished observations. Cited by: Wills JH. Pharmacological antagonists of the anticholinesterase agents. In: Koelle GB, ed. *Cholinesterase and Anticholinesterase Agents*. Berlin, Germany: Springer Verlag; 1963: 897.

129. Robinson S, Magenis TP, Minter DI, Harper H. The effects of varying doses of atropine on temperature regulation of men and dogs. In: Robinson S, ed. *The Physiological Effects of Atropine and Potential Atropine Substitutes*. Edgewood Arsenal, Md: Medical Research Laboratories; 1953. Medical Laboratory Contract Report 15.

130. Sidell FR, Markis JE, Groff WA, Kaminskis A. Enhancement of drug absorption after administration by an automatic injector. *J Pharmacokinet Biopharm.* 1974;2:197–210.

131. Vale JA, Meredith TJ, Heath A. High dose atropine in organophosphorus poisoning. *Postgrad Med J.* 1990;66:881.

132. Chew LS, Chee KT, Yeo JM, Jayaratnam FJ. Continuous atropine infusion in the management of organophosphorus insecticide poisoning. *Singapore Med J.* 1971;12:80–85.

133. LeBlanc FN, Benson BE, Gilg AD. A severe organophosphate poisoning requiring the use of an atropine drip. *Clin Toxicol.* 1986;24:69–76.

134. Wilson IB. Acetylcholinesterase, XI: Reversibility of tetra ethylpyrophosphate inhibition. *J Biol Chem.* 1951;190:111–117.

135. Wilson IB, Ginsburg S. A powerful reactivator of alkyl phosphate-inhibited acetylcholinesterase. *Biochim Biophys Acta*. 1955;18:168–170.

136. Quinby GE. Further therapeutic experience with pralidoximes in organic phosphorus poisoning. *JAMA.* 1964;187:202–206.

137. Quinby GE, Clappison GB. Parathion poisoning. *Arch Environ Health.* 1961;3:538–542.

138. Quinby GE, Loomis TA, Brown HW. Oral occupational parathion poisoning treated with 2-PAM iodide (2-pyridine aldoxime methiodide). *N Engl J Med.* 1963;268:639–643.

139. Rosen FS. Toxic hazards: Parathion. *N Engl J Med.* 1960;262:1243–1244.

140. Jacobziner H, Raybin HW. Parathion poisoning successfully treated with 2-PAM (pralidoxime chloride). *N Engl J Med.* 1961;265:436–437.

141. Funckes AJ. Treatment of severe parathion poisoning with 2-pyridine aldoxime methiodide (2-PAM). *Arch Environ Health.* 1960;1:404–406.

142. Durham WF, Hayes WJ Jr. Organic phosphorus poisoning and its therapy. *Arch Environ Health.* 1962;5:21–47.

143. Sundwall A. Minimum concentrations of N-methylpyridinium-2-aldoxime methane sulphonate (P2S) which reverse neuromuscular block. *Biochem Pharmacol.* 1961;8:413–417.

144. O'Leary JF, Kunkel AM, Jones AH. Efficacy and limitations of oxime-atropine treatment of organophosphorus anticholinesterase poisoning. *J Pharmacol Exp Ther.* 1961;132:50–57.

145. Calesnick B, Christensen JA, Richter M. Human toxicity of various oximes. *Arch Environ Health.* 1967;15:599–608.

146. Sidell FR, Groff WA. Intramuscular and intravenous administration of small doses of 2-pyridinium aldoxime methochloride to man. *J Pharm Sci.* 1971;60:1224–1228.

147. Swartz RD, Sidell FR. Renal tubular secretion of pralidoxime in man. *Proc Soc Exp Biol Med.* 1974;146:419–424.

148. Swartz RD, Sidell FR. Effects of heat and exercise on the elimination of pralidoxime in man. *Clin Pharmacol Ther.* 1973;14:83–89.

149. Josselson J, Sidell FR. Effect of intravenous thiamine on pralidoxime kinetics. *Clin Pharmacol Ther.* 1978;24:95–100.

150. Josselson J, Sidell FR. *Dose-Response Effects of Intravenous Thiamine Hydrochloride on Pralidoxime Pharmacokinetics in Man*. Edgewood Arsenal, Md: Biomedical Laboratory; 1977. EB-TR 116117.

151. Jeevarathinam K, Ghosh AK, Srinivasan A, Das Gupta S. Pharmacokinetics of pralidoxime chloride and its correlation to therapeutic efficacy against diisopropyl fluorophosphate intoxication in rats. *Pharmazie.* 1988;43:114–115.

152. Quinby GE. Further therapeutic experience with pralidoximes in organic phosphorus poisoning. *JAMA*. 1964;187:114–118.

153. Kewitz H, Nachmansohn D. A specific antidote against lethal alkylphosphate intoxication, IV: Effects in brain. *Arch Biochem Biophys*. 1957;66:271–283.

154. Loomis T. Distribution and excretion of pyridine-2-aldoxime methiodide (PAM), atropine and PAM in sarin poisoning. *Toxicol Appl Pharmacol*. 1963;5:489–499.

155. Jager BV, Stagg GN, Green N, Jager L. Studies on distribution and disappearance of pyridine-2-aldoxime methiodide (PAM) and of diacetyl monoxime (DAM) in man and in experimental animals. *Bull Johns Hopkins Hosp*. 1958;102:225–234.

156. de la Manche IS, Verge DE, Bouchard C, Coq H, Sentenac-Roumanou H. Penetration of oximes across the blood brain barrier: A histochemical study of the cerebral cholinesterase reactivation. *Experientia.* 1979;35:531–532.

157. Fleisher JH. Directorate of Medical Research, Biomedical Laboratory, Edgewood Arsenal, Md. Personal communication, 1970s.

158. von Bredow J. Major, Medical Service Corps, US Army; Directorate of Medical Research, Biomedical Laboratory, Edgewood Arsenal, Md. Personal communication, 1970s.

159. Wills JH, McNamara BP, Fine EA. Ventricular fibrillation in delayed treatment of TEPP poisoning. *Fed Proc.* 1950;9:136.

160. Valero A, Golan D. Accidental organic phosphorus poisoning: The use of propranolol to counteract vagolytic cardiac effects of atropine. *Isr J Med Sci.* 1967;3:582–584.