Chapter 5

NERVE AGENTS

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INTRODUCTION

Nerve agents, secretly developed for military use before World War II, work by inhibiting cholinesterase (ChE). Though similar chemicals are used in areas such as medicine, pharmacology, and agriculture, they lack the potency of military agents, which are extremely toxic. The military stockpiles of several major world powers are known to include nerve agents, and other countries undoubtedly possess nerve agents as well. Terrorist organizations have used nerve agents to cause mass injury and death, as was the case in the 1994 and 1995 Aum Shinrikyo subway attacks in Japan. Other groups, like Al-Qaeda, have indicated strong interest in obtaining these compounds. Therefore, it is imperative that military medical personnel are familiar with these agents, their effects, and the proper therapy for treating casualties.

HISTORY

The earliest recorded use of nerve agents comes from west Africa, where the Calabar bean, from the plant *Physostigma venenosum*, was used as an "ordeal poison" to combat witchcraft. Tribal members accused of practicing witchcraft were forced to ingest the beans and if they survived, they were proclaimed innocent.[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] resulting in its dual nomenclature.

Five organophosphorus compounds are generally regarded as nerve agents. They include tabun (North Atlantic Treaty Organization military designation GA), sarin (GB), soman (GD), cyclosarin (GF), and VX (no common name). More recently, a Soviet-developed substance closely related to VX, called VR or Russian VX, has been added to the list. The agents in the "G" series were allegedly given that code letter because they originated in Germany; the "V" in the latter series allegedly stands for "venomous." GF is an old agent, an analog of sarin, which was previously discounted 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. The toxicity and speed of action of this agent still merits consideration of it as a threat.

The first organophosphorus ChE inhibitor was probably tetraethyl pyrophosphate, 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 advances in organophosphorus chemistry, but 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 below.) The reversible type, most of which are carbamates, were developed for treating conditions such as intestinal atony, myasthenia gravis (a disorder in which the immune system attacks postsynaptic acetylcholine [ACh] receptors), and glaucoma; for example, there is a documented case from 1931 of a doctor treating gastric atony with neostigmine.[1]

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 IG Farbenindustrie developed an interest in using organophosphorus compounds as insecticides. On December 23, 1936, Gerhard Schrader, who headed the company's research effort, synthesized what is known today 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: Schrader, Ambros, Rudriger, and van der Linde.[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, Poland (part of Germany at the time), and production of tabun began 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, dismantled it, and moved it, along with key personnel, to the former Soviet Union, where production of the agents commenced in 1946.[6] Some believe the Soviets insisted on placing the border between Poland and Germany as far west as the Oder-Neisse line, where it remains today, because Stalin did not want the Dyhernfurth site, located between the Oder and Neisse rivers, to be in Germany.[7]

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] Although it is unclear why they were never used, possible explanations include Hitler's distaste for chemical warfare given his own exposure to mustard gas in World War I; Germany's loss of air superiority on the battlefield by the time sufficient nerve agent stocks were available; and Germany's mistaken belief that the Allies had also developed nerve agents.

In the waning days of World War II, troops of the United States and the United Kingdom captured some of the German munitions, which were being stored at Raubkammer, a German testing facility. The weapons, which contained an agent unknown to scientists in the United Kingdom and the United States, were taken to the each of the countries for examination. Over a single weekend, a small group of scientists at the United Kingdom 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.[8]

Use of these weapons probably would have been devastating and might have altered the outcome of the war. The Germans had tested nerve agents on inmates of concentration camps, not only to investigate their intoxicating effects but also to develop antidotes.[9] Many casualties, including some fatalities, were reported among the plant workers at Dyhernfurth. However, 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 UK studies,[8] and much of the basic knowledge about the clinical effects of nerve agents comes from research performed in the decades immediately following World War II.

Soman was synthesized in 1944 by Richard Kuhn of Germany, who was attempting to develop an insecticide.[6] Although small amounts were produced for the military, development had not proceeded far by the end of the war. The nerve agent VX was first synthesized in the 1950s by a chemical company in the United Kingdom looking for new pesticides.[6] It was then 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 synthesized around 1949 by a foreign chemist searching for alternative 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 manufacturing GB to manufacturing GF when the precursors of GB 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 United States placed these two nerve agents in M55 rockets; land mines; 105-mm, 155-mm, and 8-in. projectiles; 500-lb and 750-lb bombs; wet-eye bombs (which have liquid chemical ["wet"] contents); spray tanks; and bulk containers.[10] These munitions were stored at six depots within the continental United States and one outside the continent,[11] near the following locations: Tooelle, Utah; Umatilla, Oregon; Anniston, Alabama; Pine Bluff, Arkansas; Newport, Indiana; Richmond, Kentucky; and Johnston Island in the Pacific Ocean.

The United States signed the Chemical Weapons Convention in 1996, and it came into effect in 1997. Under its provisions, the United States pledged to eliminate its stockpile of chemical weapons, including the nerve agent stockpiles. The overseas stockpile, moved from Europe and Asia to Johnston Island, has been completely destroyed at the time of this writing. On-site destruction facilities either exist or are being built at all of the depots in the continental United States. The timetable for destruction of these stockpiles accelerated after the 2001 terrorist attacks because the depots are seen as potential terrorist targets. The largest stockpile was kept at Tooele, Utah, and was the first to be completely destroyed.

The former Soviet Union had a stockpile of chemical weapons, including nerve agents, estimated to be ten times the size of the US stockpile. Russia has pledged to eliminate this stockpile.

Nerve agents, although developed for World War II in Germany, were not used on the battlefield until 50 years later. During the Iran-Iraq War, Iraq used large quantities of tabun and sarin against Iranian forces, causing between 45,000 and 120,000 casualties, depending upon the source.[12] In 1995 Iraq declared to the United Nations Special Commission that the country still possessed 4 metric tons of VX and up to 150 metric tons of sarin. At the time, the United Nations Special Commission suspected that Iraq had up to 200 metric tons of each. As of this writing, no Iraqi stockpiles of chemical weapons have been found; however, in May 2004, two US soldiers were exposed to sarin in Baghdad, Iraq, in the form of an old Iraqi weapon that was being used as part of

an improvised explosive device.[13] There have been reports that Iran may have developed nerve agents and used them against Iraq, but these reports have never been confirmed.

Sarin has also been used in terrorist attacks. In June 1994 members of a Japanese cult released sarin from the rear of a van in Matsumoto, Japan. Although there were almost 300 casualties, including 7 deaths, this event was not well publicized. On March 20, 1995, the same group broke open plastic containers of sarin on several Tokyo trains during the morning commute. The containers held a 30% solution of liquid sarin, which the cult members synchronously ripped open on three subway trains and allowed to spill onto the seats and floors. 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 commitment of medical resources to triage and care for the casualties. (For more information on the Aum attacks, see Chapter 2, History of Chemical Warfare and Chapter 4, History of the Chemical Threat, Chemical Terrorism, and Its Implications for Military Medicine).

PHARMACOLOGY OF CHOLINESTERASE INHIBITORS

Cholinesterase in Tissue

According to the current, widely accepted explanation, nerve agents are compounds that exert their biological effects by inhibiting the enzyme acetylcholinesterase (AChE). The cholinergic system is the only neurotransmitter system known in which the action of the neurotransmitter is terminated by an enzyme, AChE.

AChE 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 choline esters, ACh, the neurotransmitter of the cholinergic portion of the nervous system, is most relevant to nerve agent activity.

AChE, found at the receptor sites of tissue innervated by the cholinergic nervous system, hydrolyzes ACh rapidly. It has one of the highest known enzyme turnover numbers (number of molecules of substrate that it turns over per unit time).[14] A similar enzyme with ACh as its preferred substrate is found in or on erythrocytes (red blood cells) and is known as red blood cell, or true, cholinesterase (RBC-ChE). Butyrylcholinesterase (BuChE, also known as serum or plasma cholinesterase and as pseudocholinesterase), another enzyme of the ChE family, uses butyrylcholine as its preferred substrate. Butyrylcholine is present in plasma or serum and in some tissues.

BuChE and RBC-ChE are the two forms of ChE in the blood. While there is a single gene for each form of ChE, the active sites are identical regardless of the physical form. However, because blood is easy to draw, 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 to an AChE inhibitor.

Cholinesterase-Inhibiting Compounds

Most ChE-inhibiting compounds are either carbamates or organophosphorus compounds. The best known 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 to manage myasthenia gravis; ambenonium was developed later for the same purpose. Pyridostigmine bromide (Mestinon, manufactured by ICN Pharmaceuticals, Costa Mesa, Calif) has been used for decades to manage myasthenia gravis. On any given day, an estimated 16,000 patients in the United States take pyridostigmine bromide medication to treat myasthenia gravis. The US military 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 below). Today these carbamates are mainly used for treating glaucoma and myasthenia gravis. Other carbamates, such as carbaryl (Sevin, manufactured by Bayer, Leverkusen, North Rhine-Westphalia, Germany), are used as insecticides.

Recently, several anticholinesterase drugs have been used to treat Alzheimer's disease, in which cholinergic transmission is faulty. In the past few years, these have become the basis of treatment of early stages of this disease. Three are approved for this indication by the US Food and Drug Administration (FDA): donepezil, rivastigmine, and galanthamine. Rivastigmine is a carbamate, donepezil is a piperidine compound, and galanthamine is a tertiary alkaloid. All inhibit ChEs.

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 phos-

phorofluoridate (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 to treat glaucoma, but later was deemed unsuitable because it produced 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; nerve agents disable the off switch for cholinergic transmission, producing cholinergic overactivity or cholinergic crisis. 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,[14,15] though the relevant aspects are summarized here.

The human nervous system is made up of conducting cells, or neurons, whose primary mission is to convey information from place to place via efficient electric signals or action potentials. When a signal reaches the end of a neuron, it can only continue as a chemical signal, the secretion of a packet of neurotransmitter molecules and its diffusion across the space or synaptic cleft separating its parent neuron from the next cell in series. When the neurotransmitter molecule reaches the target cell, it interacts with specific postsynaptic receptors on the receiving cell's surface membrane, giving rise to a miniature endplate potential. Once sufficient numbers of these are generated, they summate and a new action potential is created, allowing information transmission to proceed. Each neuron in the nervous system uses only one neurotransmitter for this purpose. The neuroanatomy of each neurotransmitter system is specific; neurons in particular tracts or regions use specific neurotransmitters. Approximately 20 neurotransmitters have been identified in neurobiology. The portion of the nervous system that uses ACh as its neurotransmitter is referred to as the cholinergic system. It is the most widely distributed and best studied in neurobiology.

Cholinergic tracts are found in almost every part of the brain within the central nervous system (CNS). Within the peripheral nervous system, however, the cholinergic system is found only in very specific fiber tracts. Clinically, the most important of these are the sympathetic and parasympathetic divisions of the autonomic nervous system.

The cholinergic nervous system can be further divided into the muscarinic and nicotinic systems, because the structures that are innervated have receptors that recognize two false experimental transmitters, alkaloids muscarine and nicotine, and can be stimulated by these compounds. In the periphery, where cholinergic input is primarily autonomic, muscarinic sites are innervated by postganglionic parasympathetic fibers. In the periphery, 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 predominantly found at the autonomic ganglia and skeletal muscles.

The brain contains a high number of cholinergic neurons. Both muscarinic and nicotinic receptors are active in the central cholinergic system, with muscarinic receptors predominating in a ratio of roughly 9 to 1. Clinically, the most important characteristic of the central cholinergic system is that it is the most anatomically widespread of any known neurotransmitter system in human brain. Consequently, a chemical, such as nerve agent, that affects the cholinergic system as a whole will affect all parts of the brain rather than only a few, as in more restricted neurotransmitter systems such as the dopaminergic or serotoninergic systems.

When an action potential in a cholinergic neuron reaches the terminal bouton, ACh packets are released, cross the synaptic cleft, interact with postsynaptic cholinergic receptors, and cause a new action potential to be generated. The cycle continues until ACh is hydrolyzed by AChE, a membrane-bound protein. This is the mechanism that prevents cholinergic stimulation from getting out of hand (Figure 5-1).

In the cholinergic nervous system, ChE hydrolyzes the neurotransmitter ACh to terminate its activity at the receptor site (Figure 5-2). The catalytic mechanism of AChE involves first an acylation step, in which serine 203 reacts with ACh to displace the choline moiety and forming an acylated serine (the choline, having been displaced, diffuses away). This reaction is greatly facilitated by other strategically placed residues in the active site that orient the ACh to the appropriate angle for serine to displace the choline and stabilize the transition state by a three-pronged hydrogen bond (the "oxyanion hole"). In a second step, a water molecule bound to, and polarized by, another key amino acid residue, histidine 447, attacks the acyl group, displacing it from the serine to form acetic acid, which diffuses away and leaves a regenerated or reactivated enzyme that can repeat the operation.

If AChE is absent from the site, or if it is unable to function, ACh accumulates and continues to produce postsynaptic action potentials and activity in the organ. The nerve agents and other ChE-inhibiting substances

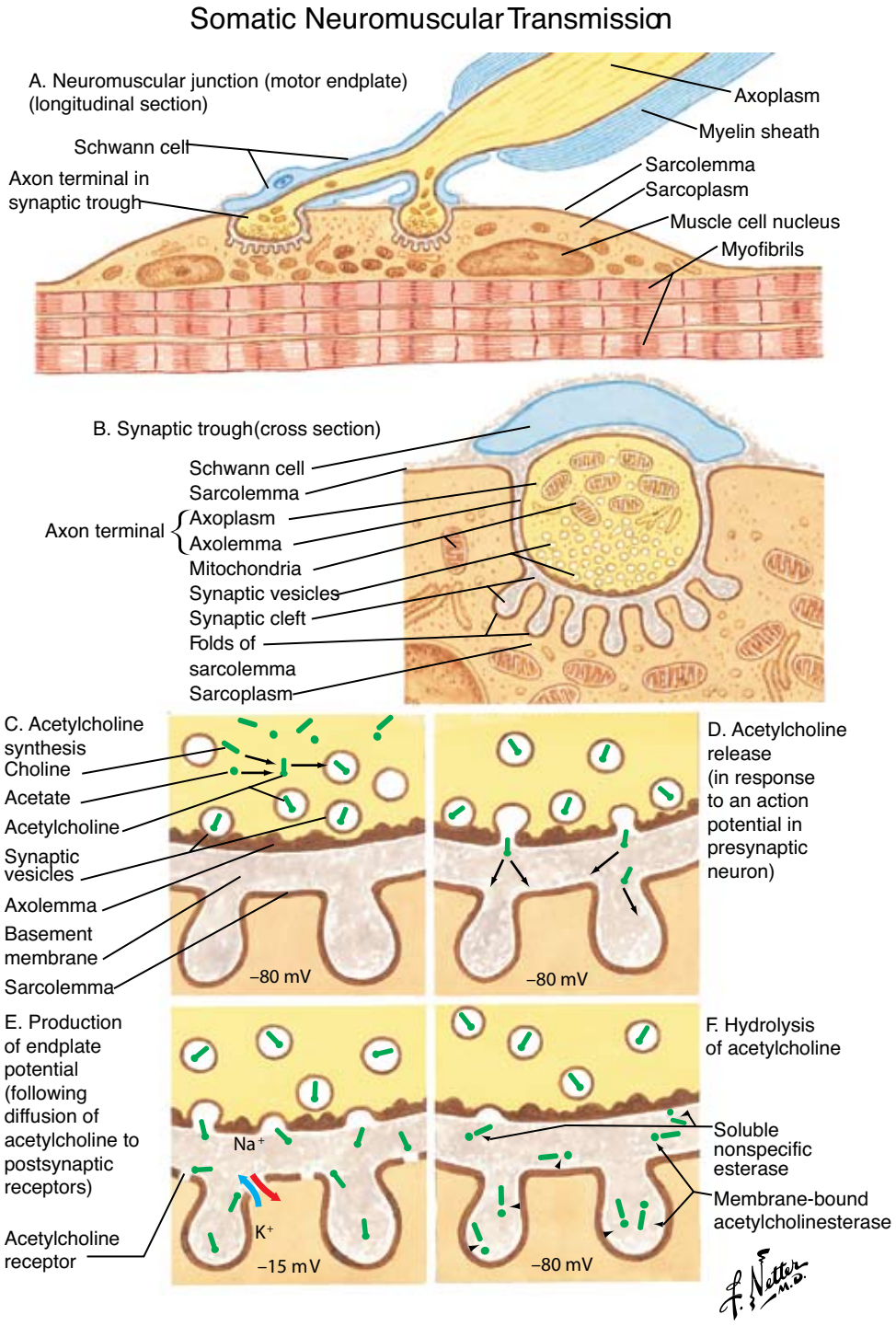

Fig. 5-1. Diagram of neuromuscular conduction. **(a)** Nerve fiber with axon terminal in synaptic trough of muscle. **(b)** Close-up of axon terminal in trough, with synaptic vesicles indicated. **(c)** Acetylcholine synthesis from acetate and choline and storage of acetylcholine in synaptic vesicles. **(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.
Reproduced with permission from: *Clinical Symposia*. 1948;1(1§8):162. Plate 3118. West Caldwell, NJ: CIBA-GEIGY Medical Education Division.

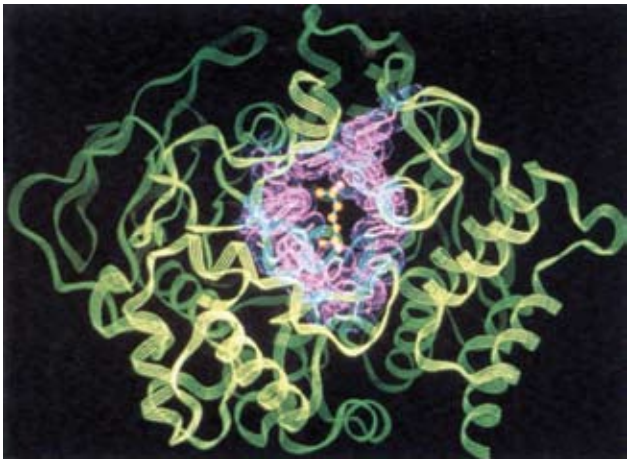

Fig. 5-2. This schematic ribbon diagram shows the structure of Torpedo californica acetylcholinesterase. The diagram is color-coded; green: the 537-amino acid polypeptide of the enzyme monomer; pink: the 14 aromatic residues that line the deep aromatic gorge leading to the active site; and gold and blue: a model of the natural substrate for acetylcholinesterase, the neurotransmitter acetylcholine, docked in the active site.
Reproduced 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.

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. The resulting toxidrome is referred to as cholinergic crisis.

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 an hour after reacting with physostigmine and for 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 that case, enzymatic activity returns only with the synthesis of new enzyme. Functionally then, organophosphorus compounds may be said to be irreversible inhibitors of ChE, whereas the carbamates cause only temporary inhibition and are therefore referred to as reversible inhibitors.

Because 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. A previously administered ChE inhibitor will, in a manner of speaking, protect the enzyme from a second one.[16,17] 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 (see below).

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.[18,19] An individual severely exposed to soman, however, was alert and functioning reasonably well for several days while ChE activity in his blood was undetectable (Exhibit 5-1).[20] This case study and other data suggest that tissue function is restored at least partially when ChE activity is still quite low.

Blood Cholinesterases

Individuals 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 must 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 ChE activity. If the activity is 90% or more of the worker's baseline, no action is taken. If the activity is below 90% of the baseline, the sample is rerun. If the second test also indicates activity below 90% of baseline, the individual is referred to the oc-

EXHIBIT 5-1

CASE REPORT: ACCIDENTAL EXPOSURE OF A MAN TO LIQUID SOMAN

This 33-year-old man [who worked at Edgewood Arsenal, Edgewood, Maryland] had been working with small amounts of soman in solution [25% (V/V) concentration, total volume <1 mL] when a syringe-needle connection broke, splashing some of the solution into and around his mouth. . . He immediately washed his face and rinsed his mouth with water and was brought to the emergency room about 9 AM, 5-10 min after the accident. He was asymptomatic until he arrived at the ER when, as he later said, he felt "the world was caving in on me," and he collapsed. His past medical history was noncontributory. Physical examination showed him to be comatose and mildly cyanotic with slightly labored respirations. Intravenous atropine sulfate (2 mg) was given and may have been partially responsible for his initial blood pressure of 180/80 and heart rate of 150. He had miosis (1-2 mm, bilaterally), markedly injected conjunctiva, marked oral and nasal secretions, moderate trismus and nuchal rigidity, prominent muscular fasciculations, and hyperactive deep-tendon reflexes. Except for tachycardia, his heart, lungs, and abdomen were normal.

Within a minute after he collapsed (about 10 min after exposure) he was given intravenous atropine sulfate and in the ensuing 15 min he received a total of 4 mg intravenously and 8 mg intramuscularly, and pralidoxime chloride (2-PAMCl) was administered (2 gm over a 30 min period in an intravenous drip). Supportive care in the first 30 min consisted of oxygen by nasal catheter and frequent nasopharyngeal suction. Bronchoconstriction and a decreased respiratory rate and amplitude were prominent; the former was more responsive to atropine therapy. He became cyanotic and attempts to insert an endotracheal tube were unsuccessful because of trismus. Since spontaneous respiration did not cease, a tracheostomy was not performed.

After the initial therapy his cyanosis cleared and his blood pressure and heart rate remained stable. He began to awaken in about 30 min and thereafter was awake and alert. Migratory involuntary muscular activity (fasciculations and tremor) continued through the day.

He improved throughout the day, but was generally uncomfortable and restless with abdominal pain and nausea throughout the day and night. Atropine (4 mg, i.v.) was required again at 11 PM (14-hr post exposure) after several episodes of vomiting. About 4 AM, he was catheterized because of urinary retention.

His restlessness and intermittent nausea continued, and about 5 AM (20 hr after exposure) he again vomited. Because the previous atropine had apparently caused urinary retention, this emesis was treated with a small dose (5 mg, i.m.) of prochlorperazine, although phenothiazines have been reported to be deleterious in anticholinesterase compound poisoning. His general condition, including his discomfort, did not change.

He vomited twice more between 7:30-8 AM (22-23 hr post exposure) and was again given atropine (4 mg, i.m.). He voided small amounts several times, but catheterization was necessary several hours later.

Several EKGs recorded on admission and during the first day showed sinus tachycardia. On the second day (25 hr after exposure and about 2 hr after atropine administration), his cardiac rhythm was irregular, and an EKG showed atrial fibrillation with a ventricular rate of 90-100 beats per min. This persisted throughout the day and evening, but his cardiac rhythm was again regular sinus the next morning.

During the second evening (about 36 hr after exposure), he again became nauseated and had recurrent vomiting. Because of the occurrences of urinary retention and arrhythmia, presumably due to atropine, he was again given prochlorperazine (5 mg, i.m.) at 10 PM and again at 2 AM. Half an hour after the first he complained of transient "tingling" feelings over his body, but there were no objective changes. After the second he rested comfortably and slept soundly for 3-4 hr, his first restful sleep since the exposure. At 11 AM the next morning, he was restless and had an expressionless face, torticollis, and athetoid movements. Diphenylhydramine hydrochloride (50 mg, i.v.) promptly relieved these symptoms and signs, which are characteristic of the extrapyramidal side effects of a phenothiazine. Throughout the remainder of his hospitalization, the patient's physical condition improved although he was treated with sulfisoxazole for three weeks for a urinary tract infection that developed after catheterization.

His psychiatric condition did not improve as rapidly as his physical condition. As the complications of the treatment for the physical effects subsided, evidence of lingering mental effects began to appear. A psychiatrist . . . who saw the subject frequently, recorded that he seem depressed, was withdrawn and subdued, admitted to antisocial thoughts, slept restlessly and fitfully, and had bad dreams. On the third day [after the exposure] the patient was given scopolamine hydrobromide (5 μg/kg, or 330 μg, i.m.) as a therapeutic trial. Psychiatric evaluation at the time of maximum scopolamine effect showed a slight but distinct improvement in mental status as he seemed more comfortable and performed better on several mental function tests (eg, serial 7s) than before scopolamine. That evening he was given 1.8 mg of scopolamine (orally) at bedtime and slept much better for most of the night.

This nighttime benefit from scopolamine may have occurred because of its sedative properties, but the improvement in mental status during the day suggested a more specific action, as scopolamine in this dose produces a slight decrease in intellectual functioning in normal subjects. [Thereafter, scopolamine and methscopolamine (which does not enter the central nervous system) were admin-

(Exhibit 5-1 *continues)*

Exhibit 5-1 *continued*

istered on randomly assigned days. The patient did better mentally (by examination) and on a written arithmetic test after receiving scopolamine than after methscopolamine.]

There was no detectable RBC-ChE until about the tenth day after exposure. . . . Apparently neither the RBC nor plasma ChE was significantly reactivated by the initial oxime therapy, which reflects the rapid irreversible phosphorylation and hence refractoriness of the soman-inhibited enzyme to reactivation by oxime.

Hematocrit, hemoglobin, white blood cell count, prothrombin time, blood urea nitrogen, bilirubin, creatinine, calcium, phosphorus, serum glutamic oxaloacetic transaminase, alkaline phosphatase, sodium, potassium, chloride, and carbon dioxide were all within normal limits the day of admission and on repeated measurements during his hospitalization.

About five weeks after his admission, the subject again received scopolamine (5 mg/kg, i.m.) and had a decrement in mental functioning, including a 25-30% reduction in NF [Number Facility] scores, which are the findings in normal subjects. This contrasts with the paradoxical improvement in mental status seen earlier.

About a week later, the psychiatrist noted that "he is probably close to his premorbid level intellectually and there is no evidence of any serious mood or thinking disorder."

A battery of standard psychological tests was given the subject 16 days, 4 months, and 6 months after the accident. He scored well on the Wechsler-Bellevue IQ test with a slight increase in score on the arithmetic section at the later testings. He had high Hs (hypochondriasis) and Hy (hysteria) scales on the Minnesota Multiphasic Personality Inventory (MMPI) on the early test and their later improvement indicated to the examiner that he had a decreased concern about bodily function. He did poorly on a visual retention task (the object of which was to remember and then reproduce a simple drawing) on first testing as he attempted to improve already correct drawings, made several major errors, and showed poor motor control; his later tests were normal. On word association, proverbs, and the ink blot he was slow and sometimes used delaying tactics, had difficulty generating verbal associations, and failed the harder proverbs, responses that in the examiner's opinion were not consistent with his IQ. The results of his later tests were faster, imaginative, and indicated full use of his intellectual facilities.

When last seen, six months after his exposure, the patient was doing well.

Reproduced with permission from Sidell FR. Soman and sarin: clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol*. 1974;7:1–17.

cupational health physician for review to determine if the depression in RBC-ChE activity is related to exposure to ChE-inhibiting substances. If RBC-ChE is depressed to 75% or below baseline, the worker is considered to have had an exposure and is withdrawn from work. Investigations are undertaken to discover how the worker was exposed. Although workers may be asymptomatic, they are not permitted to return to a work area around nerve agents until their RBC-ChE activity is higher than 90% of their baseline activity.[21] If workers have symptoms from a possible nerve agent exposure or if an accident is known to have occurred in their work area, RBC-ChE activity is immediately measured and the criteria noted above, as well as signs and symptoms, are used for exclusion from and return to work. The values of 75% and 90% were selected for several reasons, including the following: (a) the normal variation of RBC-ChE in an individual with time; (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 (see below).

In training responders to deal with acute nerve agent poisoning, little emphasis should be given to the use of laboratory diagnosis of ChE activity. Time does not permit using this determination to guide immediate treatment. On the other hand, laboratory values in patients are particularly helpful in two specific instances: (1) as a screen for exposure to a ChE inhibitor, as in agricultural workers or military personnel who may have been exposed to a nerve agent, and (2) as a way to follow exposed patients as they recover over time.

Butyrylcholinesterase

The enzyme BuChE is present in blood and throughout tissue. Its physiological role in humans is unclear[22]; however, it may be important in canine tracheal smooth muscle,[23] the canine ventricular conducting system,[24] and rat atria.[25]

BuChE is synthesized in the liver and has a replace-

ment 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.[22] This enzyme has no known physiological function in blood, but may assist in hydrolyzing certain choline esters.

People who have a prolonged paralysis caused by succinylcholine, a muscle relaxant, usually have low BuChE activity.[22] 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.[22] In addition to having the low BuChE activity in the usual assay (as a result of this genetic abnormality), people 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%.[26] There are over 20 variants of the abnormal BuChE phenotype, each with different, low dibucaine numbers, including zero.

The relationship of BuChE activity and succinylcholine can be somewhat different. One author[27] reports on an individual whose BuChE activity was 3 times 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,[22] but one report[28] 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

Butyrylcholinesterase

In longitudinal studies[29,30] 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 both men and women. Of the ranges (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.[30]

BuChE activity does not vary with age in women[31,32] until the age of 60 years, when higher BuChE activities are seen.[32] 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.[32–34]

Erythrocyte Cholinesterase

RBC-ChE activity is more stable than the activity of the BuChE.[30,35,36] In a study[30] 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,[31] RBC-ChE activity was unchanged with age, while in another,[32] 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 effective scavengers of nerve agents while they remain in the circulation. There is little inhibition of tissue enzyme until much of the blood enzyme is inhibited because, with the exception of local tissue effects (eg, eye, respiratory tract, skin contact), the blood is the first tissue to encounter the agent. The RBC-ChE appears to correlate more closely with tissue ChE and physiological signs of poisoning than the plasma enzyme in this regard. In two studies,[37,38] 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 below). In humans, some pesticides, such as parathion,[39–41] systox,[39] and malathion,[22] also preferentially inhibit the plasma enzyme, while others, such as dimefox[41] and mevinphos,[42] initially bind with the RBC enzyme. In animals, there appears to be a species difference because parathion preferentially inhibits RBC-ChE in rats and the plasma enzyme in dogs.[22]

The nerve agent VX preferentially inhibits RBC-ChE; in two studies,[43,44] 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,[37,45] 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).[46] 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.[43,44]

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[44] 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,[47] 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,[48] 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 decontaminated. 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.

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,[43] both the maximal inhibition of RBC-ChE activity and the appearance of signs and symptoms occurred about 1 hour after intravenous (IV) 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. There appears to be no correlation between the severity of these effects and the blood ChE activity. Early experimental data[49–51] 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).[52] More recently, clinical data from the Tokyo incident has shown that symptoms and signs can both be present with normal blood ChE levels.[53]

Minimal systemic effects, such as vomiting, occur in half the population when the RBC-ChE is inhibited to 25% of its control activity.[43,44] In a study[44] 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

TABLE 5-1

RELATION OF EFFECTS OF NERVE AGENT EXPOSURE TO ERYTHROCYTE CHOLINESTERASE ACTIVITY

Effect	Patients Affected (N=62)	Range of RBC-ChE Activity (% of Baseline*)
Miosis alone (bilateral)	22	0–100
Miosis alone (unilateral)	7	3–100
Miosis and tight chest	12	28–100
Miosis and rhinorrhea	9	5–90
Miosis, rhinorrhea, and tight chest	9	20–92
Rhinorrhea and tight chest	3	89–90

*Cholinesterase activity before nerve agent exposure.
RBC-CHE: red blood cell cholinesterase.
Data source: Sidell RF. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. San Diego, Calif: Academic Press; 1992: 163.

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, the authors observed that patients had an RBC-ChE activity of 0% without the expected symptoms; this inhibition was acutely induced.

Data from 283 individuals who received VX by various routes are categorized below (Table 5-2). 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."[14(p446)]

TABLE 5-2

RELATION OF CHOLINESTERASE ACTIVITY TO VOMITING AFTER EXPOSURE TO VX

Minimum RBC-ChE (% of Baseline*)	Patients (N=283)	Patients Vomiting	Percentage Vomiting
> 50	166	1	0.6
40–49	24	2	8.3
30–39	27	9	33.3
20–29	42	19	45.2
< 20	24	16	66.7

*Cholinesterase activity before nerve agent exposure
RBC-ChE: red blood cell cholinesterase.
Data sources: (1) Sidell FR, Groff WA. The reactivatibility of cholinesterase inhibited by VX and sarin in man. *Toxicol Appl Pharmacol*. 1974;27:241–252. (2) 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.

Nerve Agents

Molecular models of the nerve agents tabun, sarin, soman, and VX are shown in Figure 5-3. The chemical, physical, and environmental properties of these compounds are summarized in Table 5-3. Nerve agents differ from commonly used ChE inhibitors

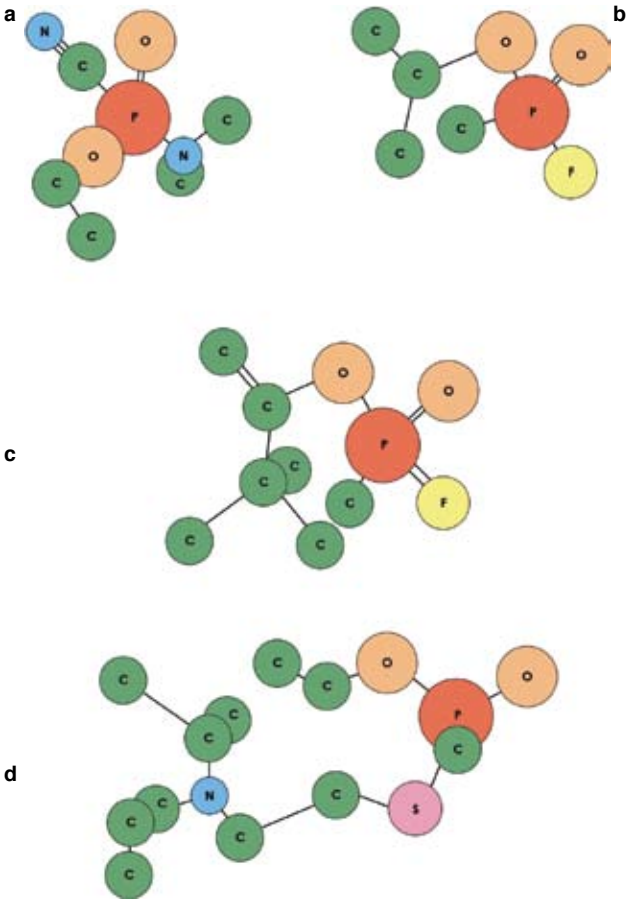

Fig. 5-3. Molecular models of **(a)** Tabun (GA), **(b)** Sarin (GB), **(c)** Soman (GD), **(d)** VX.
Molecular models: Courtesy of Office E Clark, Researcher, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

TABLE 5-3

CHEMICAL, PHYSICAL, AND ENVIRONMENTAL 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	0.037mm Hg at 20°C	2.1 mm Hg at 20°C	0.40 mm Hg at 20°C	0.0007 mm Hg at 20°C
Density				
Vapor (compared to air, air = 1)	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	Fruity	Odorless	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 papers	M8, M9 papers	M8, M9 papers	M8, M9 papers
Persistency				
In soil	Half-life 1–1.5 days	2–24 hours at 5°C–25-°C	Relatively persistent	2–6 days
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

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

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[45] with ChE from human erythrocytes, brain, and muscle showed that sarin had about 10 times more inhibitory activity than TEPP, 30 times more than neostigmine, 100 times more than DFP, and 1,000 times more than parathion.

The nerve agents are liquid at moderate temperatures (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, cyclosarin, VR, and VX are apparently odorless.

One of the US soldiers exposed to sarin in Iraq in 2004 reported to the authors that the agent smelled like garbage, but that may have been due to impurities.

Cyclosarin (GF) and VR are not as well studied as the other agents. In animal tests GF has a toxicity intermediate between sarin and tabun, while VR has the same level of toxicity as VX.

The G agents are volatile; VX and VR have very low volatility. Sarin, the most volatile, is somewhat less volatile than water; tabun, cyclosarin, and soman are less volatile than sarin. The G agents present a definite vapor hazard; VX and VR are much less likely vaporize 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 or protected from the vapor, but they may continue to worsen if the exposure continues. There is no delay in onset as there is after liquid exposure.

At low C*t* values (the concentration to which an organism is exposed to a substance times the amount of time the organism is exposed; Exhibit 5-2), the eyes, nose, airways, or a combination 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, a combination 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, possibly 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, 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 to the authors that he noticed an increase in secretions and difficulty breathing, and another said he felt giddy and faint before losing consciousness. In both instances, the casualties were unconscious within 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; labored, irregular, and gasping breathing; generalized

EXHIBIT 5-2

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

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

- 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.
- Because C*t* is a product of C times *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 ($Ct = 5\ mg/min/m^3$ in both cases). This generalization is usually invalid for very short or very long times, however, because an organism may hold its breath for several seconds and not actually inhale the vapor, or some detoxification may occur over many hours.
- 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.

TABLE 5-4

EFFECTS OF EXPOSURE TO NERVE AGENT VAPOR

Amount of Exposure	Effects*
Small (local effects)	Miosis, rhinorrhea, slight bronchoconstriction, secretions (slight dyspnea)
Moderate (local effects)	Miosis, rhinorrhea, slight bronchoconstriction, secretions (moderate to marked dyspnea)
Large	Miosis, rhinorrhea, slight bronchoconstriction, secretions (moderate to marked dyspnea), loss of consciousness, convulsions (seizures), generalized fasciculations, flaccid paralysis, apnea, involuntary micturition/defecation possible with seizures

*Onset of effects occurs within seconds to several minutes after exposure onset.

TABLE 5-5

EFFECTS OF DERMAL EXPOSURE TO LIQUID NERVE AGENTS

Level of Exposure	Effects
Mild	
Effects may be precipitant in onset after an asymptomatic interval of up to 18 hours	Increased sweating at the site Muscular fasciculations at site
Moderate	
Effects may be precipitant in onset after an asymptomatic interval of up to 18 hours	Increased sweating at the site Muscular fasciculations at site Nausea Diarrhea Generalized weakness
Severe	
Effects may be precipitant in onset after a 2–30 minutes asymptomatic interval	Increased sweating at the site Muscular fasciculations at site Nausea Diarrhea Generalized weakness Loss of consciousness Convulsions (seizures) Generalized fasciculations Flaccid paralysis Apnea Generalized secretions Involuntary micturition/defecation possible with seizures

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.

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 symptoms and signs may occur even if the casualty has been decontaminated.[48]

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-minute 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, the authors observed flaccid paralysis and apnea in both individuals.

The major clinical differences between the inhalational and dermal routes of exposure are the following:

- Miosis and respiratory involvement are almost invariant with inhalational exposure, but may be delayed or even absent in dermal

exposure.
- The speed of onset and progression of symptoms will be far faster in inhalational exposure.
- Decontamination of dermal exposure may not occur before agent has penetrated the skin, and consequently patients who are treated for nerve agent symptoms after dermal exposure may subsequently worsen as agent becomes available systemically. This is not likely with inhalational exposure.

Exposure to nerve agent liquid through a wound will likely produce effects intermediately.

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 example, there is a plethora of data from animal studies and studies in isolated neuromuscular preparations for the musculoskeletal system, but study results are difficult to apply to a human clinical situation. The two terrorist attacks using sarin in Japan in 1994 and 1995 have provided a fund of new human clinical data, but this data is all uncontrolled. The Japanese terrorist and Iranian battlefield clinical experience is summarized in a later section of this chapter.

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 perioral) exposure to a nerve agent might be large enough to produce moderate symptoms (nausea, vomiting) without miosis. In studies[43,44,47] 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.[54] 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

TABLE 5-6

EFFECTS OF NERVE AGENTS IN HUMANS

Organ or System	Effect
Eye	Miosis (unilateral or bilateral), conjunctival injection; pain in or around the eye; complaints of dim or blurred vision
Nose	Rhinorrhea
Mouth	Salivation
Pulmonary tract	Bronchoconstriction and secretions, cough; complaints of tight chest, shortness of breath; wheezing, rales, and/or rhonchi on exam
Gastrointestinal tract	Increase in secretions and motility; nausea, vomiting, diarrhea; complaints of abdominal cramps, pain
Skin and sweat glands	Sweating
Muscular	Fasciculations ("rippling"), local or generalized; twitching of muscle groups, flaccid paralysis; complaints of twitching, weakness
Cardiovascular	Decrease or increase in heart rate; usually increase in blood pressure
Central nervous system	Acute effects of severe exposure: loss of consciousness, convulsion (or seizures after muscular paralysis), depression of respiratory center to produce apnea Acute effects of mild or moderate exposure or lingering effects (days to weeks) of any exposure: forgetfulness, irritability, impaired judgment, decreased comprehension, a feeling of tenseness or uneasiness, depression, insomnia, nightmares, difficulty with expression

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. RBC-ChE activity, then, 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 C*t* 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. For the same reason, miosis is the most likely symptom to persist after all systemic effects of nerve agent have resolved.[52]

Unilateral miosis is sometimes seen in workers handling nerve agents or insecticides and usually occurs because of a small leak in the eyepiece of 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 (depth perception). This impairment may cause difficulty in activities such as driving a car or piloting an airplane, which require stereo-visual coordination (the Pulfrich stereo effect).[22]

Miosis may begin within seconds to minutes of the start of exposure; if the concentration of agent vapor or aerosol is 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).[20,55]

The effects of nerve agents on vision have been studied for decades.[56] Characteristically, an unprotected individual exposed to nerve agent will have the signs discussed above and may complain of dim vision, blurred vision, or both.

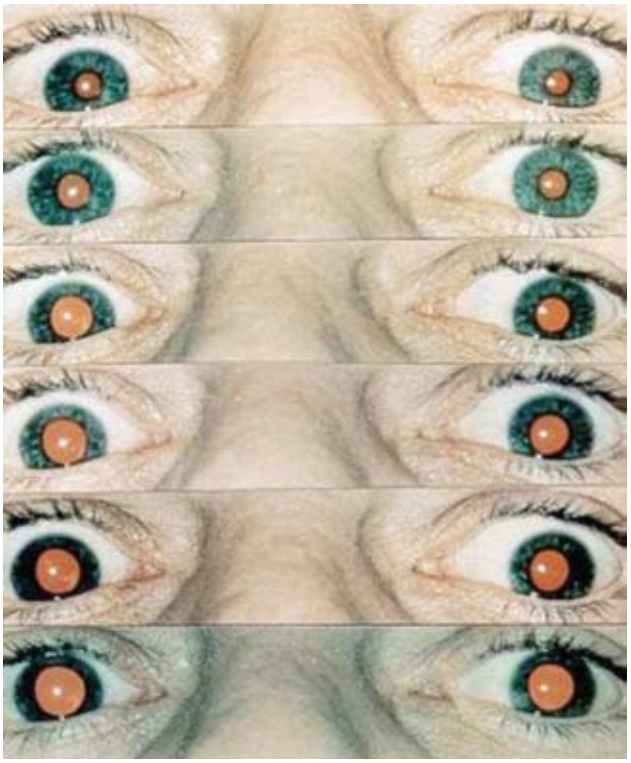

Fig. 5-4. This man was accidentally exposed to an unknown amount of nerve agent vapor. The series of photographs shows his eyes gradually recovering their ability to dilate. All photographs were taken with an electronic flash (which is too fast for the pupil to react) after the subject had been sitting 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.
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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[57] 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 miosis improved, which suggests that factors other than a small pupil are responsible for the high light threshold.[58] In another study,[59] 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 miosis did not occur. The threshold was reduced to normal following systemic administration of atropine sulfate (which enters the CNS), but not after administration of atropine methyl-nitrate (which does not enter the CNS).[60] The authors suggested that the dimness of vision was due to neural mechanisms in the retina or elsewhere in the CNS.

Although the dim vision reported by individuals exposed to nerve agent vapor is generally ascribed to miosis, the above accounts suggest that central neural

EXHIBIT 5-3

CASE REPORT: EXPOSURE OF THREE MEN TO SARIN

Three men [who worked at Edgewood Arsenal, Edgewood, Maryland], ages 27, 50, and 52 years, were brought to the emergency room because of sudden onset of rhinorrhea and slight respiratory discomfort. At the onset of symptoms they were working in a large room in which some containers of sarin were stored. Although there were other workers in the room, the three patients were together at one end where a leak was later found in one of the containers.

On examination all three patients had essentially the same signs and symptoms: very mild respiratory distress, marked miosis and slight eye pain, rhinorrhea, a moderate increase in salivation, and scattered wheezes and rhonchi throughout all lung fields. No other abnormal findings were noted.

All three patients reported that their respiratory distress had decreased since its onset about 20 min before they arrived at the emergency room. The men were kept under observation for the next 6 hr, but no therapy was administered. They continued to improve and at the time of discharge from the ward they were asymptomatic except for a slight irritation in the eyes and decreased vision in dim light.

The patients were seen the next day and at frequent intervals thereafter for a period of four months. Each time they were seen, their [blood cholinesterase activities (both erythrocyte cholinesterase and butyrylcholine esterase)] were measured . . . and photographs were taken of their eyes [see Figure 5-4]. The first photographs were taken the day of the exposure, but the patients were not dark adapted. On each visit thereafter a photograph was taken by electronic flash after the man had been in a completely dark room for 2 min. . . . About 60-70% of the lost ability to dark adapt returned in two weeks, but complete recovery took two months.

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mechanisms may have equal or greater importance. In the case of the carbamate physostigmine, an increase in light sensitivity (a decreased threshold) after intramuscular (IM) administration of the drug has been reported.[61] 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. 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

Individuals exposed to nerve agents sometimes complain of blurred as well as dim vision. In one study,[62] visual acuity was examined in six subjects before and after exposure to sarin vapor at a C*t* of 15 $mg/min/m^3$. Near visual acuity was not changed in any of the subjects 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 after exposure. As the effects of the agent decreased, their vision returned to its previous state, which took about 35 days.[55] 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.[62]

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 told the authors that the secretions were much worse than those produced by a cold or hay fever.

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

The pulmonary effects of nerve agent poisoning are crucial, probably the most important component of the nerve agent poisoning toxidrome. A nerve agent death is almost always a pulmonary death, whether from bronchoconstriction, bronchorrhoea, central apnea, paralysis of the muscles of respiration, or, in most cases, a combination of all of these. Military medics are trained to focus on respiratory status as the most important parameter of the effectiveness of treatment in nerve agent poisoning.

After exposure to a small amount of nerve agent vapor, individuals often complain of a tight chest (difficulty breathing), which is generally attributed to spasm or constriction of the bronchiolar musculature. Secretions from the muscarinically innervated 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, 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).[63] Some observers found increases in airway resistance[64] and other changes, while other researchers did not.[65]

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 are usually 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. Clinically, this resembles a severe asthmatic attack.

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. The authors observed that 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. 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[66] 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 apneic and will die as a result of ventilatory failure, which precedes circulatory system collapse. Three major factors contribute to respiratory failure: obstruction of air passages by bronchoconstriction and by respiratory secretions; weakness followed by flaccid paralysis of the intercostal and diaphragmatic musculature 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[67] describing original studies in nine species. The authors of the report 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[68] 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,[69] bronchoconstriction seen in the dog after IV sarin administration was quite severe compared with that in the monkey. Dogs have thick airway musculature, which may explain that finding. Differences in circulatory and respiratory effects were seen between anesthetized and unanesthetized dogs given sarin.[70] 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[71] 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 review[72] 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[67]). Respiratory failure was the predominant cause of death in the species studied because significant cardiovascular depression occurred only after cessation of respiration.[71,72] 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.[67,71]

In one study,[73] pyridostigmine was administered to primates, which were then 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). 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 from 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 does not appear to enter the CNS, it is suggested 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 the animals' central nervous systems, but it is not found in the brains of normal animals after they receive 2-PAM Cl.[74]

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 are normally painless, and small fasciculations often escape the patient's notice. 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; the patient is not likely to notice these if the area affected is small. Fasciculations can also 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. Fasciculations will typically 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 or become momentarily 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 has been a matter of debate. 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 has pipetted soman into his or her mouth; see Exhibit 5-1).[20] Nerve agents also produce convulsions that are associated with frank epileptiform seizure activity as measured by EEG recordings.[75–77] In cases of severe poisoning, convulsive movements and associated epileptiform seizure activity may stop or become episodic as respiratory status becomes compromised and oxygenation is depressed. It may be impossible to clinically distinguish convulsive activity because of frank central seizures from the purely peripheral neuromuscular symptoms

of jerks and tremor.

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. In the Aum Shinrikyo attacks of 1995, some patients complained of effects lasting longer, even months.[78] Whether these are direct nerve agent effects, posttraumatic stress disorder, or a combination is not known. Common complaints include feelings of uneasiness, tension, 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 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. Several of the findings on behavioral and psychological changes that occur following exposure to nerve agents or pesticides have recently been summarized.[79,80]

Studies of Behavioral and Psychological Changes

In one of the earliest studies of the effects of ChE-inhibiting substances,[38] behavioral and psychological changes were reported in 49 of 60 subjects (of whom 50 were normal and 10 had myasthenia gravis) after daily IM 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 of the study 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.[81,82]

One report[66] suggests that several workers accidentally exposed to sarin had some behavioral effects. Another report[72] 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[58] 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 report 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 report 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.[58]

In a series[83] of 72 workers exposed to sarin, two reported difficulty in concentration, five reported mental confusion, five reported giddiness, and four reported insomnia. All but two of these individuals were considered to have been exposed to a small amount of sarin; they 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[84] 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 < 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. But no measurements were taken between 8 and 24 hours, and the maximal inhibition might have been in this period. Often it is overlooked that there may be a long delay between exposure on the skin and onset of signs or symptoms. The study authors stressed that psychological impairment might occur before the onset of other signs or symptoms or might occur in their absence.[84]

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 tension, 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 (subtracting from 100 by 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 5-1).[20] 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 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 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.[85,86] No decrements were found on physical tasks[87] (at a C*t* of 14.7 mg/min/m^3). On a military field exercise,[88] most tasks were performed satisfactorily, if suboptimally, in the daylight. Nighttime performance, however, was difficult, if not hazardous due to a miosis-induced decrement in dark adaptation and subsequent visual acuity.

The behavioral effects of exposure to nerve agents or other potent organophosphorus compounds in humans can be conceptually grouped into three classes: effects on cognitive processes, effects on mood or affect, and disturbances of sleep-wakefulness. This cluster of CNS and behavioral effects of nerve agents is consistent with what is known about the role of ACh and cholinergic neurons within the brain. Central cholinergic circuits are involved in both cognition and short-term memory, as demonstrated by the effects of drugs,[89] experimentally produced lesions,[90] and naturally occurring pathological states of cholinergic insufficiency (such as Alzheimer's disease).[91] It has also been hypothesized for a number of years that depression is due to an imbalance between the cholinergic and adrenergic systems within the brain, and that depressive symptoms are associated with cholinergic hyperactivity.[92–94] Finally, sleep cycle control, specifically the initiation and maintenance of the rapid eye movement (REM) stage of sleep, the sleep stage that is associated with dreaming, is controlled by increased activity of cholinergic neurons within specific nuclei in the pontine brain stem.[95–98] Administration of carbamates, organophosphorus anticholinesterase compounds, or cholinergic agonists that act like nerve agents can induce REM sleep in both animals and humans.[98–102]

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,[103] 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, IV).

In another study,[104] 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[45] in which subjects were exposed to smaller amounts of sarin, the EEG changes coincided with severity of symptoms. With mild symptoms, voltage was slightly diminished. 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, IV).

The effects of various anticholinesterase agents (nerve agents, other organophosphorus compounds, and carbamates) on EEG activity were reviewed and the study authors proposed that a three-stage change is produced in the normal EEG of animals or humans by progressively higher doses of these compounds.[105] At Stage I an activation pattern is produced in the EEG that is characterized by a low amplitude desynchronized pattern of mixed frequencies normally seen in alert subjects. This pattern is induced regardless of the subject's behavioral state when the anticholinesterase is administered, and may last from minutes to several hours, depending upon the dose and the type of compound. This pattern is associated with an approximately 30% to 60% inhibition of RBC-AChE, which is comparable to levels of inhibition associated with minimal to mild signs or symptoms of exposure. This level of ChE inhibition may also be associated with some mild, short-term effect on REM sleep.

The Stage II EEG pattern is marked by a continuation of the activation pattern seen during Stage I, with intrusions of high-voltage, slow-frequency (delta, theta) waves and an increased amount of high frequency (beta) waves. The Stage II pattern is associated with mild to moderate signs or symptoms of intoxication in both human and animal studies. These EEG changes may persist for hours or days, depending upon the severity of the dose, and are associated with approximately 60% to 80% inhibition of RBC-AChE. Such levels of exposure are also expected to produce a moderate increase of REM.

Stage III EEG changes are associated with the most severe levels of exposure and are represented by epileptiform activity in a variety of patterns. This is typically marked by very high-voltage waves, with low-frequency delta waves being most prominent. There are marked signs of agent intoxication, as well as seizure and convulsive activity, that require immediate pharmacological treatment. Animal studies show that all nerve agents are potent convulsant compounds that can elicit prolonged seizure activity that has all the clinical and electrophysiological features of status epilepticus.[76,77,106,107] Seizure activity in human victims of severe nerve agent exposure is typically of limited duration, due to the rapid compromise in respiratory status and associated decrease in oxygenation.

Following such severe exposures, EEG changes may persist for months to years, depending upon the severity of the initial insult and possibly upon the rapidity and effectiveness of pharmacological treatment. Long-term EEG effects show up as isolated spikes, sharp waves, or both during sleep or drowsiness, or with hyperventilation.[46,103,108–110] Such severe EEG and neurobehavioral effects are associated with initial levels of RBC-AChE inhibition greater than 70%. The effects of such severe exposures on REM sleep are prominent and can persist for weeks or months after the exposure. In experimental animal studies, unchecked, nerve-agent–induced seizures can persist over a period of many hours, and can result in brain damage and long-term neurobehavioral changes. Both the brain damage and neurobehavioral effects can be blocked or minimized by rapid treatment with appropriate anticonvulsant medications.[77,111]

Long-Term Effects

Long-term effects on the human CNS after poisoning with nerve agents or organophosphorus insecticides have been reported.[20,79,80,112,113] These reports are based on clinical observations, occasionally supported by psychological studies. In general, the behavioral effects have not been permanent but have lasted weeks to several months, or possibly several years.[114] A distinction needs to be made between these more transient effects that represent reversible neurochemical changes of nerve agents on brain function and those more permanent effects described below.

In the early 1980s, several laboratories reported that animals that survived high-dose exposure to nerve agents developed brain lesions.[115–117] Similar findings had been reported by Canadian researchers in technical reports in the 1960s.[118,119] Further studies confirmed these initial findings and led to several hypotheses as to the cause of these brain lesions. First, some authors suggested that the nerve agents may produce a direct neurotoxic effect on brain neurons.[115,120] Second, the pattern of brain damage seen in these nerve-agent–

exposed animals was similar to that seen after hypoxic encephalopathy. Because nerve-agent–exposed animals exhibit varying durations of respiratory distress, several authors hypothesized that nerve-agent–induced hypoxia was primarily responsible for producing these lesions.[116,118,119] A third hypothesis was that the lesions were the consequence of the prolonged seizures experienced by the animals during the intoxication.[121]

Subsequent work both in vivo[122] and in vitro[123] has failed to demonstrate support for the hypothesis that nerve agents are directly neurotoxic. Likewise, the overwhelming evidence that effective treatment of nerve-agent–induced seizures can block or significantly reduce the extent of brain lesions argues against the direct neurotoxicity hypothesis.[77]

There is conflicting evidence regarding the possible role of hypoxia as an etiologic factor in brain damage following seizure activity, whether nerve agents or other chemoconvulsants cause this seizure activity. 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 close to 50 mm Hg did not have brain lesions, whereas those with normal air intake and partial pressure of arterial oxygen higher than 128 mm Hg developed brain lesions.[124] 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[125] (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.

The hypothesis that prolonged seizure activity is primarily responsible for nerve-agent–induced brain damage in experimental animals has now become well accepted.[77] Studies in rats have shown that brain damage development requires a minimum duration of continuous seizure activity.[124,125] Seizures terminating before 10 minutes have elapsed resulted in no observable damage. In animals that seized for 20 minutes before seizures were stopped, about 20% experienced mild amounts of damage in restricted foci. In contrast, in animals that experienced 40 minutes of seizure before seizures were stopped, over 80% experienced damage, and this damage was more severe and widespread than the 20-minute-treatment group. Studies in nonhuman primates confirm that delay in seizure control increases subsequent brain pathology.[126,127] Studies with effective drugs that can stop nerve agent seizures (benzodiazepines, anticholinergics, N-methyl-D-aspartate antagonists) by many research groups have overwhelmingly demonstrated that seizure control protects experimental animals (rats, guinea pigs, nonhuman primates) from developing brain damage.[107,128–137]

There are, however, experimental studies that show that convulsion development following nerve agent exposure does not invariably lead to brain damage and, conversely, that some animals that never display convulsions develop brain lesions. All of these studies used observational procedures to determine presence of convulsive/seizure activity following nerve agent exposure. While nonconvulsive/nonseizure-mediated neuropathology may have been observed following exposure to nerve agents, the exact neuropharmacological mechanism(s) that might produce this damage has yet to be described.

In addition to having morphologically detectable brain lesions, animals surviving severe nerve agent intoxication have been shown to have decrements in performance, as measured on a variety of behavioral tests.[136–140] These decrements were apparent in some studies for at least 4 months, when the last survivors were sacrificed. These animals, mostly rats, are reported to display other persistent behavioral changes (hyperresponsiveness, difficulties regulating body weight, spontaneous convulsions) that can also be considered consequences of the brain lesions.

In general, in untreated or inadequately treated nerve-agent–poisoned animals, convulsive (and seizure) activity usually stops shortly after respiration becomes compromised. Some of these animals die while others recover after some degree of apnea, and electrographic seizure activity, as monitored on the EEG, can resume while overt motor convulsions may no longer be apparent. Motor movements (finger twitches, repetitive arm/leg movements, nystagmus) become more subtle, of smaller amplitude, and intermittent. These bear all the same clinical characteristics as described for late-stage status epilepticus in humans.[141] In some of the reported cases of severe nerve agent intoxication in humans,[20,66,104] convulsive activity has also been brief and medical treatment was promptly available to prevent further convulsive episodes. There are several reports, however, from the Aum Shinrikyo terrorist attacks of individuals exhibiting prolonged seizure activity before adequate therapy could be delivered.[110,142] It is not known whether these victims suffered brain damage similar to that described in experimental animals, but two individuals experienced profound retrograde amnesia, one of which still displayed high-amplitude epileptiform waves in the EEG 1 year after the exposure.

Interpreting clinical studies in light of experimental results is difficult largely because the role of hypoxia is very hard to separate from any seizure-mediated

nerve agent toxicity on the human brain. Because of respiratory depression, it is possible to attribute much of the reported CNS sequelae in human victims to hypoxic damage.

A major challenge in interpreting the reports of long-lasting neurobehavioral complaints in patients who have survived nerve agent exposure is separating out that part of the syndrome that is clearly psychological, including, in many cases, posttraumatic stress disorders satisfying psychiatric criteria in *The Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, from that which is due to direct toxicity of nerve agent upon the nervous system itself. Some of these reports are summarized below.

Only one case has been reported of peripheral nerve damage after human nerve agent intoxication. In this one case, a victim of the Tokyo Aum Shinrikyo attack developed distal sensory axonopathy months after his exposure. Causality could not be established.[143]

Cardiovascular System

Little data exists on the cardiovascular effects of nerve agents in humans. In mild-to-moderate intoxication 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 the authors have observed that some atrial-ventricular (A-V) heart block (first-, second-, or third-degree) with bradycardia 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. Because treatment initiation is urgent in severely intoxicated patients, electrocardiograms (ECGs) have not been performed before atropine administration. 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 transient A-V dissociation before the onset of bradycardia (which precedes 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 clinically important.

Reports of patients exposed to pesticides and the results of animal studies provide additional information about cardiovascular reactions to nerve agents. In one study,[144] dogs exposed to lethal amounts of sarin vapor had idioventricular rhythms within minutes after exposure; following atropine therapy, some of the dogs had third- degree and first-degree heart blocks before a normal rhythm returned. In another study,[145] 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 organophosphorous pesticide poisoning.[146]

Dogs were instrumented to examine the cardiac changes occurring for a month after IV administration of 2 LD_{50} of soman.[147] Atropine and diazepam were administered shortly after soman exposure to control seizure activity. During the study period, there was increased frequency of episodes of bradycardia with ventricular escape, second-degree and third-degree heart block, and independent ventricular activity (single premature beats, bigeminy, or runs of ventricular tachycardia).

In a similar study,[148] rhesus monkeys were given the standard military regimen of pyridostigmine before exposure to soman (1 LD_{50}, IM), 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[145] and after organophosphorus pesticide poisoning in humans.[149] Torsade de pointes is a ventricular arrhythmia, usually rapid, of multifocal origin, which on ECG 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. Recent studies have shown that sarin-exposed rats display pronounced QT segment prolongation for several weeks after near-lethal exposures, and that these animals showed an increased sensitivity to epinephrine-induced arrhythmias for at least 6 months after exposure.[150]

In addition to the arrhythmias described above, studies have shown that animals (rats, nonhuman primates) severely poisoned with nerve agents can develop frank cardiac lesions.[125,131,151–154] The early stage (15 minutes–several hours) of these lesions consists of

hypercontraction and hyperextension of sarcomeres, focal myocytolysis, and the development of contraction bands that are the result of the breakdown of markedly hypercontracted myofibril bundles. This is followed by an inflammatory response (24 hours or less), which begins with edema and neutrophil infiltration and ends with mononuclear cell infiltration and scavenging of necrotic sarcoplasm by macrophages. This is followed by a stage of repair (72 hours or less), which begins with a proliferation of fibroblasts and ends with myofiber loss and replacement fibrosis. Some studies have shown a relationship between the development of seizures following nerve agent exposure and the occurrence and severity of cardiac lesions.[131]

Ventricular fibrillation, a potentially fatal arrhythmia, has been seen after administration of a ChE inhibitor and atropine. It can be precipitated by the IV administration of atropine to an animal that has been rendered hypoxic by administration of a ChE inhibitor.[155,156] Although this complication has not been reported in humans, atropine should not be given intravenously until the hypoxia has been at least partially corrected.

Because of the well-recognized possibility that ventricular fibrillation can occur in a hypoxic heart given atropine, many intensive care unit physicians and nurses are reluctant to give the large amounts of atropine that may be required to treat acute nerve agent poisoning. The authors have observed that this issue has come up in several training exercises. Although data are fragmentary, the literature suggests that the chance of death from acute nerve agent poisoning is greater than the chance of ventricular fibrillation from atropine on a hypoxic heart, at least in initial field management. Once the patient has reached a hospital setting where proper monitoring is possible, it should be less problematic to administer atropine safely in the amounts required while giving oxygen as necessary.

Heart Rate

Although it is frequently stated that a patient intoxicated with a nerve agent will have bradycardia, this is not proven 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 beats per minute, 41 with heart rates of 81 to 89 beats per minute, 38 with heart rates of 90 to 99 beats per minute, and 31 with heart rates higher than 100 beats per minute. A heart rate of 64 to 80 beats per minute is considered normal in adults.[157] 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 beats per min).

Reports of the heart rates of patients severely intoxicated by insecticides vary. In a report[158] describing 10 patients (9 of whose consciousness was moderately-to-severely impaired), 7 presented with heart rates over 100 beats per minute, and the other 3 had heart rates over 90 beats per minute (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,[159] the heart rates of three unconscious patients were slow (one had cardiac arrest). Two acutely ill, unconscious patients were described in a comprehensive review of organophosphorus poisoning[54]; one had a heart rate of 108 beats per minute, the other 80 beats per minute. 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 it is often forgotten or overlooked.

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

The first and perhaps most important aspect of treating acute nerve agent poisoning is decontaminating the

patient. Decontamination is performed to prevent the casualty from further absorbing the agent or to keep the agent from spreading further on the casualty or to others, including medical personnel, who may come into contact with the casualty.

Ventilatory Support

Ventilatory support is a necessary aspect of therapy to save a casualty with severe respiratory compromise. Antidotes alone may be effective in restoring ventilation and saving lives in some instances. In animal studies,[160,161] antidotes alone, given intramuscularly at the onset of signs, were adequate to reverse the effects of agent doses of about 3 times 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.

Breathing impairment 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. In a severely poisoned person, breathing ceases completely within several minutes after the onset of exposure.

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.[66]

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 H2O or lower, and the secretions diminish (although they may thicken), creating less obstruction to ventilatory efforts. Thus, in the unlikely but conceivable situation that a lone first responder must treat a severely poisoned casualty whose heart is still beating, IM atropine should be administered first (because it only takes a few seconds) before attempting to intubate and resuscitate the patient.

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, and only a few—the mask-valve-bag ventilation 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, 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 to this 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 smaller hazard. Studies[162–164] 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.

When managing a mass casualty incident, planners need to understand that the period of time that ventilatory support will be necessary in nerve agent casualties is much shorter than that required for severe organophosphate insecticide poisoning. This is because organophosphate insecticides tend to be more fat-soluble than nerve agents, disappear into the fat stores, and off-gas, causing symptoms, for days. Despite the greater toxicity of nerve agents, ventilatory support should only be required for hours at most. Nerve agents also differ greatly in this respect from both pulmonary oedemagenic agents, such as chlorine and phosgene, and from sulfur mustard. Casualties of both of these types of agents may require ventilatory support for days to weeks.

In the Aum Shinrikyo subway attack in Tokyo, only four of 640 patients seen at Saint Luke's International Hospital for definite or suspected sarin poisoning required intubation for ventilatory support. Of the four patients, one died with severe hypoxic encephalopathy

on hospital day 28, and was intubated throughout the course. Of the remaining three patients, representing the most severe cases who survived, intubation was required only for 24 hours or less. This shows that mechanical ventilation in essentially all cases who survive sarin poisoning is a short-term clinical concern.[165]

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[20,66]; 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.[166] 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.[167]

Cholinergic blocking substances act by blocking the effects of excess ACh at muscarinic receptors. ACh 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 muscarinic 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.

Several countries use, or have proposed to use, other anticholinergic drugs as adjuncts to atropine for treating nerve agent poisoning. These anticholinergics have much more potent and rapid effects on the CNS than does atropine. For example, Israel uses a mixture of drugs known as TAB as their immediate nerve agent treatment. This mixture contains the oxime TMB-4, atropine, and the synthetic anticholinergic benactyzine. From 1975–1980 the US military also used TAB. The atropine and benactyzine combination in the TAB mixture is similar in composition to the atropine, benactyzine and 2-PAM combination antidote mixtures investigated by Yugoslav researchers in the early 1970s.[168,169] Animal studies have shown that benactyzine is much more potent and acts more rapidly to reverse the CNS effects of nerve agent intoxication than does atropine.[170,171] In addition, benactyzine is significantly less potent in inhibiting sweating or producing mydriasis than atropine, and is therefore less likely to induce heat casualties in a warm environment or compromise near vision in the case of accidental use. Military researchers in the Czech Republic have advocated the use of the synthetic anticholinergics benactyzine and trihexyphenidyl, along with the carbamate pyridostigmine, in a prophylactic mixture they have designated as PANPAL.[172] In addition, the Czechs utilize benactyzine and biperiden, as well as atropine, as postexposure antidotal treatments.[172,173]

While many countries have other anticholinergic drugs to use as adjuncts to atropine to treat nerve agent poisoning, none of these compounds have been tested or used in human clinical cases of poisoning either with nerve agents or other organophosphate or carbamate pesticides.

Nevertheless, atropine has been the antidote of choice for treating nerve agent intoxication since nerve agents were first discovered and produced during World War II. It was included in the German nerve agent first aid kits[174] and was determined to be an effective antidote by British scientists at Porton Down who first analyzed the pharmacology and toxicology of tabun obtained from captured German artillery shells. Since the 1940s, atropine has been adopted as the first-line antidote to counteract nerve agent poisoning by the armed forces of most countries. It is also almost universally used as the antidote to treat anticholinesterase poisoning by organophosphate or carbamate pesticides.[175,176]

A dose of 2 mg atropine was chosen for self -administration or buddy-administration (the AtroPen automatic injector included in the Mark I (Meridian Medical Technologies Inc, Bristol, Tenn) kit contains 2 mg; Figure 5-5) by the US and the military of several other countries because it reverses the effects of nerve agents, the associated side effects of a dose this size can be tolerated, and reasonably normal performance

Fig. 5-5. The Mark I kit with its two autoinjectors: the AtroPen containing 2 mg atropine, labeled 1—indicating it is to be injected first—and the ComboPen containing 600 mg 2-pyridine aldoxime methyl chloride (2-PAM Cl), labeled 2—indicating it is to be injected second. The plastic clip keeps both injectors together and serves as a safety for both devices. The kit is kept in a soft black foam holder that is carried in the gas mask carrier.
Reproduced with permission from: Meridian Medical Technologies Inc, Bristol, Tenn.

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 desirable 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 is not usually noticed by the recipient), a dry mouth, dry skin, mydriasis, and some paralysis of accommodation. Most of these effects will dissipate in 4 to 6 hours, but near vision may be blurred for 24 hours, even in healthy young patients. 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 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.[177]

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,[178] 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 (versus 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 more convenient to use than the needle and syringe, and it results in 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.

The FDA has recently approved a combined-dose autoinjector including both atropine and 2-PAM Cl. Bioequivalence was demonstrated in animal studies. The dose of atropine in the new product, designated by the Department of Defense as the antidote treatment nerve agent autoinjector (ATNAA), is 2.1 mg (Figure 5-6). At the time of writing, this product awaits a production contract with an FDA-approved manufacturer; it is anticipated that the ATNAA will replace the older MARK 1 kit by approximately 2008. Its tactical value

Fig. 5-6. The antidote treatment nerve agent autoinjector (ATNAA) delivers 2.1 mg atropine and 600 mg 2-pyridine aldoxime methyl chloride (2-PAM Cl). The medications are in separate compartments within the device and are expressed out of a single needle. The gray cap on the right end of the injector is the safety.
Reproduced with permission from: Meridian Medical Technologies Inc, Bristol, Tenn.

lies in halving the time to administer the two antidotes compared to the MARK 1 kit.

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 become less hyperactive. However, unless given in very large doses, IV or IM atropine does not reverse miosis caused by nerve agent vapor in the eyes. A casualty with miosis alone should not be given atropine, and pupil size should not be used to judge the adequacy of atropine dosage.

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-minute 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 until secretions are minimized (those in the mouth can be seen and those in the lungs can be heard by auscultation), and until resistance to ventilatory efforts is minimized (atropine decreases constriction of the bronchial musculature and airway secretions). If the casualties are conscious, they 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 30 minutes to 3 hours after exposure.[20,66] The authors have observed several recovering casualties without non-life-threatening, adverse effects (such as nausea and vomiting) 24 to 36 hours after exposure for which atropine was administered.[20] However, there appears to be no reason to give atropine routinely in this period.

In the only battlefield data that have been published, Syed Abbas Foroutan reported using atropine much more aggressively and in larger amounts.[12] After an initial IV test dose of 4 mg atropine, he waited 1 to 2 minutes. If there was no sign of atropinization, he gave another 5 mg IV over 5 minutes while checking the pulse. He titrated his dose to pulse rate, accelerating if the heart rate dropped to 60 beats per minute to 70 beats per minute and decreasing it for pulse rates over 110 beats per minute. This resulted in doses of atropine, in some cases, up to 150 mg IV in 5 minutes. US doctrine, by contrast, uses a 6-mg IM loading dose followed by 2-mg increments until IV access is established. Foroutan's protocol may reflect the pressure of having large numbers of casualties to treat, the relative lack of availability of oximes, particularly far forward, and his inability to guarantee that atropine could be continually administered during evacuation to the next echelon of medical care.

In contrast with nerve agent treatment, 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.[179–181] Medical care providers must recognize that the amount of atropine needed for treating insecticide poisoning is different than the amount needed for treating nerve agent poisoning. Pesticides may be sequestered in the body because of greater fat solubility 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). This point is crucial in training personnel who are used to seeing insecticide poisonings to manage nerve agent casualties. Insecticide casualties may require intensive care unit beds for days; nerve agent casualties almost never do and are usually either dead or well enough to require minimal medication within 24 hours.

There has recently been increased discussion about the endpoints of atropinization and the most efficient means to achieve it. The textbook recommendations for early atropinization from various authors have been assessed using model data of atropine dose requirements in patients severely poisoned with organophosphate pesticides.[175] These authors concluded that a dose-doubling strategy, continued doubling of successive doses, would be the most rapid and efficient way to achieve atropinization. Likewise, the treatment regimen used by Foroutan[12] would also result in a rapid atropinization. The endpoints of atropinization recommended by Army Field Manual 8-285, *Treatment of Chemical Agent Casualties*,[182] the *Medical Management of Chemical Agent Casualties Handbook*,[183] Foroutan,[12] and Eddleston et al[175] are very similar: lack of bronchoconstriction, ease of respiration, drying of respiratory secretions, and a heart rate > 80 to 90 beats per minute.

The goal of therapy with atropine should be to minimize the effects of the agent (ie, to remove casualties from life-threatening situations and make them 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 (one at Edgewood Arsenal, Maryland, in 1969 and one at Dugway Proving Ground, Utah, in 1952), unconscious, almost immediately after taking one or two breaths, and 4 to 5 minutes later they were flaccid and apneic.[20,66] Even at very low concentrations, maximal effects occur within minutes of exposure termination. 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 or ATNAA. 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.

If a casualty is seen immediately after exposure from vapor only, the contents of one Mark I kit or ATNAA should be given if miosis is the only sign, the contents of two kits or injectors 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 or ATNAA for mild or moderate dyspnea, the contents of two kits or injectors for severe dyspnea (obvious gasping), and the contents of three kits or injectors 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. 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. Generally, 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 it is deciding 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.

Unlike, for example, lewisite exposure, nerve agent does not irritate the skin. 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 or ATNAA. 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 or ATNAA 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 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 or ATNAA). 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 or ATNAA), 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.[179–181]

The US military developed an inhaled form of atropine, called "medical aerosolized nerve agent antidote (MANAA)," which was approved by the FDA in 1990. It is not widely used but is still available in the national stockpile. The official doctrine for its use is as follows:

> MANAA is used mainly in medical treatment facilities by the individual casualty under medical supervision for symptomatic relief of nerve agent-induced secretions and muscle twitches. It is intended for use after the casualty has been decontaminated and evacuated to a clean environment where there is no need for MOPP, including the mask. The MANAA allows the patient to self-medicate on an "as needed" basis.[184]

MANAA has a limited role in patients recovering from nerve agent poisoning who still require some observation but who can self-medicate. It has not been stockpiled to any great extent in the civilian sector.

In hospital management of both vapor and liquid casualties, and, in many cases, in management en route to a hospital, such as in an ambulance, the preferred route of administration of atropine will be intravenous after the initial IM field doses. The clinical endpoint, that of patients breathing comfortably on their own without the complication of respiratory secretions, will be the same. A longer period of IV atropine administration should be expected in patients exposed through the skin than in vapor-exposed patients.

The management of patients exposed to nerve agent through open wounds will probably fall between that of vapor-exposed casualties and casualties exposed to nerve agent liquid on intact skin.

Oxime Therapy

Oximes are nucleophilic substances that reactivate the organophosphate-inhibited ChE (the phosphonylated enzyme) by removing the phosphyl moiety. Oximes may be considered a more physiologic method of treating nerve agent poisoning than atropine because they restore normal ChE enzyme function. However, several features limit their utility.

Mechanism of Action

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

1. The enzyme may be spontaneously reactivated by hydrolytic cleavage, which breaks the organophosphonyl–ChE bond, reactivating the enzyme.
2. The complex formed by the enzyme-ChE may lose a side group and become negatively charged, or "age," becoming 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 organophosphonyl–enzyme complex ages, it cannot be broken by an oxime.[14,15] Consequently, 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.[44,47,113] 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.[113] The half-time for aging of the tabun-enzyme complex is somewhat longer.

In the mid 1950s, Wilson and coworkers reported

that hydroxamine reactivated organophosphoryl-inhibited ChE faster than water did,[185] and later reported that an oxime (pyridine-2-aldoxime methiodide [2-PAM I]) was far more effective than hydroxamine in reactivating the enzyme.[186]

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 thoroughly studying many of these compounds, 2-PAM Cl was chosen for use in the United States.[187] The choice was made because of research in both the civilian and military sectors experimentally demonstrated effectiveness as a reactivator and also because of the demonstrated clinical efficacy of 2-PAM Cl in treating organophosphorus insecticide poisoning.[188–194] At present, the only oxime approved by the FDA for use in the United States is 2-PAM Cl. The methanesulfonate salt of pralidoxime is the standard oxime in the United Kingdom, whereas TMB4 and toxogonin (obidoxime) are used in other European countries. Japan uses pralidoxime iodide. Other oximes, not yet approved, are of interest to several countries. HI-6 is advocated by some in Canada, while newer oximes are under study in the United States.

Because oximes reactivate the ChE inhibited by a nerve agent, they might be expected to completely reverse the effects caused by nerve agents. However, because it is possible that nerve agents 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. Oximes are also quaternary drugs and have limited penetration into the CNS. For these reasons, they are ineffective in reversing the central effects of nerve agent intoxication. 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 dysfunction 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[195] 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 is little data to support or disprove this contention. The 2-PAM Cl administered with the ComboPen or MARK 1 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 male).[178]

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 IV dose of 2-PAM Cl increased from 5 to 10 mg/kg.[196] The PR increased from 1.6 to 4.2 when the IM dose of 2-PAM Cl increased from 30 to 120 mg/kg in sarin-poisoned rats,[160] and the PR increased from 1.9 to 3.1 when the IM dose of 2-PAM Cl increased from 11.2 to 22.5 mg/kg in VX-poisoned rabbits.[163] 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. When 2-PAM Cl was administered intravenously in humans 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.[113]

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 IV doses of 15 mg/kg or less, but may be marked and prolonged at higher doses.[197] 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.[197] 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 5-7).

2-PAM Cl is rapidly and almost completely excreted unchanged by the kidneys: 80% to 90% of an IM or IV

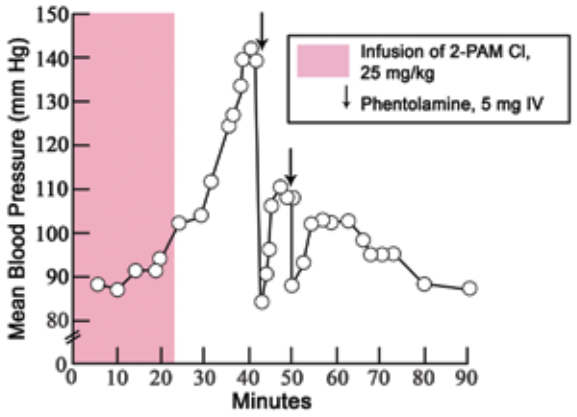

Fig. 5-7. An infusion of 25 mg/kg of 2-pyridine aldoxime methyl chloride (2-PAM Cl) over about 25 minutes produces marked hypertension, which is rapidly but transiently reversed by phentolamine (5 mg). The mean blood pressure is the diastolic plus one third of the difference between the systolic and the diastolic.
Reproduced 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.

dose is excreted in 3 hours,[198] probably by an active tubular excretory mechanism (its renal clearance is close to that of p-aminohippurate[199]), with a half-time of about 90 minutes.[144] Both clearance and amount excreted are decreased by heat, exercise, or both.[200] 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.[198–202] Some[203] question the therapeutic benefit of thiamine.

An early clinical report[204] on the use of 2-PAM Cl in insecticide-poisoned people 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 brains of animals[205,206] or the cerebrospinal fluid of humans[207] after experimental administration of 2-PAM Cl. Other investigators[74,208] found small amounts of 2-PAM Cl or reversal of the brain ChE inhibition in brains of animals poisoned with organophosphorus compounds.

Administration

An oxime should be initially administered with atropine. In cases of severe exposure, the contents of three Mark I kits or ATNAA should be administered; if these 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 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 at-risk workers caused gastrointestinal irritation, including diarrhea. It is no longer common practice for crop workers to be given 2-PAM Cl as a pretreatment either, 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 may be the best alternative in certain cases, such as that of 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 the worker's RBC-ChE activity to 80% of the baseline value, which is necessary for return to work. (See Blood Cholinesterases section, above, for discussion of monitoring RBC-ChE activity.)

Oral administration may be considered preferable (although less reliable) to administration through a parenteral route because tablets can be self-administered and taking tablets avoids the pain of an injection.

IM administration of 2-PAM Cl with automatic injectors results in a plasma concentration of 4 μg/kg at 7 minutes, versus 10 minutes for conventional needle-and-syringe injection.[178] (A maximum plasma concentration of 6.9 μg/kg occurs at 19 min, versus 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).[198,199] When given intramuscularly, 30 mg/kg caused an elevation in blood pressure and minimal ECG changes, but no change in heart rate.[198]

Because of the rapid aging of the soman–AChE complex, oximes are often said to be ineffective in treating soman poisoning. Experimental studies in animals have shown that oximes are not 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).[209,210] 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,[209] or that it causes the circulation to improve, possibly by stimulating the release of catecholamines.[210]

Because of the hypertensive effect of 2-PAM Cl, US military doctrine states that no more than 2000 mg IV or three autoinjectors (600 mg each) should be given in 1 hour. If patients require additional treatment in the interim, atropine alone is used. Thus, as the ATNAA combined autoinjector replaces the MARK 1 set, atropine-only autoinjectors should also be available for use so that the 2-PAM Cl dosage limits are not exceeded during the treatment of a severe casualty.

Anticonvulsive Therapy

Convulsions occur after severe nerve agent exposure. In reports[20,66,104] 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 given.

Laboratory studies indicate that the convulsive period lasts much longer (hours) in animals, even those given therapy, than in humans. 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 animal studies because the animals are protected from the immediate lethal effects of exposure but not the convulsant effects.

Therapy

Diazepam, an anticonvulsant of the benzodiazepine family, has been shown to control nerve-agent–induced seizures/convulsions in rats, guinea pigs, rabbits, and monkeys.[128,211–215] It is commonly used to stop acute seizures (eg, status epilepticus) that may result from other etiologies,[141] including those produced by other anticholinesterases. Experimental studies also have shown that diazepam reduces or prevents nerve-agent–induced brain lesions due to this anticonvulsant activity.[128,129,131,132,135,211] Because of these properties and because diazepam is approved by the FDA for treatment of status epilepticus seizures by the IM route, diazepam was adopted by the US military as the drug for immediate anticonvulsant treatment of nerve agent casualties in the field.

During the Persian Gulf War, the US military issued an autoinjector containing 10 mg of diazepam (Convulsive Antidote, Nerve Agent, or CANA) to all military personnel (Figure 5-8). The Convulsive Antidote, Nerve Agent injector was not intended for self-use, but rather for use by a buddy when a soldier exhibited severe effects from a nerve agent. The

Fig. 5-8. The convulsive antidote nerve agent autoinjector (CANA) contains 10 mg of diazepam. The distinctive flared "wings" on each side make the shape of the injector unique and provide visual and tactual cues to indicate it is different from either the 2-pyridine aldoxime methyl chloride (2-PAM Cl) ComboPen or the antidote treatment nerve agent autoinjector (ATNAA).
Reproduced with permission from: Meridian Medical Technologies Inc, Bristol, Tenn.

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 10 mg doses at 10-minute intervals to a convulsing casualty. Current policy states that diazepam is given following the third Mark I or ATNAAs when the condition of the casualty warrants the administration of three Mark I kits or ATNAAs. The United Kingdom uses a drug similar to diazepam known as Avizafone.[132] Avizafone is a water-soluble, prodrug formulation of diazepam that is bioconverted to diazepam following injection.

If a convulsing or seizing casualty is being treated in a medical treatment facility, research has shown that other anticonvulsant benzodiazepines (eg, lorazepam [Ativan, Wyeth, Madison, New Jersey]), midazolam [Versed, Roche, Basel, Switzerland]) are just as effective in stopping nerve-agent–induced seizure as diazepam.[138] Experimental work has also shown that midazolam is twice as potent and twice as rapid in stopping nerve-agent–induced seizures compared to diazepam when the drugs are administered IM, the route of administration for immediate field treatment.[107,211] For these reasons, efforts are currently underway for FDA approval of midazolam as treatment of nerve-agent–induced seizures and the eventual replacement of diazepam by midazolam in the convulsive antidote nerve agent injectors.

Therapy for Cardiac Arrhythmias

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

Experimental studies[156,215] have shown that when animals are poisoned with ChE inhibitors and then allowed to become cyanotic, rapid IV administration of atropine will cause ventricular fibrillation. This effect 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, this produced a pharmacologically isolated heart, with both cholinergic and adrenergic blockade. The authors reporting on the case suggested that propranolol might be of value in protecting against the effects of atropine and organophosphorus intoxication.[216]

SPECIFIC TREATMENT BY EXPOSURE CATEGORY

The goals of medical therapy of any poisoning are, in most cases, 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.

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. Topical application of atropine or homatropine can effectively relieve eye or head pain not relieved by Mark I injections.

The signs of severe distress in a fellow soldier, such as twitching, convulsions, gasping for breath, and apnea, can be recognized by an 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 provide little improvement in the presence of copious secretions and high airway resistance. 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 medications will not immediately restore consciousness or respiration or completely reverse skeletal muscle abnormalities, nor will IM or IV 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 at 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 presenting signs and symptoms.

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 and 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.

Suspected Exposure

Suspected but unconfirmed exposure to a nerve agent sometimes occurs in an area where liquid agent was present. Workers without signs or symptoms may not be sure they are 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 to measure 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.

Because the onset of effects caused by nerve agent exposure may occur as late 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.

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 munitions or a 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 systemically for miosis, if that is the only symptom, 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 or one ATNAA) may provide some relief.

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, the contents of two Mark I kits or two ATNAA should be administered 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 or ATNAA. 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 (Mark I kit) or three ATNAAs should be given; further therapy should be with atropine alone.

A person mildly exposed to a nerve agent should be thoroughly decontaminated (exposure to vapor alone does not require decontamination). The casualty should also have blood drawn to measure RBC-AChE activity prior to administering Mark I or ATTNA if facilities are available for the assay. Again, the MANAA inhaled atropine product may be helpful for patients under observation of a medic who can self-medicate.

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, and blood should be drawn for assay of RBC-ChE activity if assay facilities are available. The contents of three Mark I kits or three ATNAAs 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/ATNAAs. Additional atropine should be given at 5-minute to 10-minute intervals until the dyspnea subsides. No more than three Mark I kits or ATNAAs should be used; however, additional atropine alone should be administered if the contents of three kits or ATNAAs 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 of 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 or ATNAAs should be administered initially, and further therapy (the contents of a third Mark I kit or ATNAA to a total of three, then atropine alone) given at 5-minute 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 or ATNAA should be given initially, and additional Mark I kits or ATNAAs as needed to a total of three. Atropine alone should be used after the third Mark I or ATNAA. If the time of exposure is unknown, the contents of two Mark I kits or ATNAAs 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 or ATNAAs 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. Diazepam should always be given when the contents of three Mark I kits or ATNAAs 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, improvement should be expected. 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 IV administration of atropine, or 5 to 10 minutes after IM 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

Casualties who are severely exposed to a nerve agent will be unconscious. They may be apneic or gasping for air with marked cyanosis, and may be convulsing or postictal. These casualties will have copious secretions from the mouth and nose and will have generalized fasciculations in addition to convulsive or large-muscle twitching movements. If they are postictal, or in nonconvulsive status epilepticus, they 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, level 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. A carotid pulse may be the easiest for the examiner to feel in mission-oriented, protective posture, level 4 gear. In a medical treatment facility, the medical personnel may be slightly more optimistic and proceed with aggressive therapy. After the Aum Shinrikyo 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 via 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 casualties and to remove them 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.

Medical personnel must first 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 or ATNAAs and diazepam. If ventilatory assistance will be forthcoming within minutes, the contents of the three Mark I kits or ATNAAs 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/ATNAA 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 IM should be considered. The IV 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 may 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. In this case, because of the volume disparity, multiple atropine autoinjectors or ATNAAs are required to compensate for the volume of the tracheobronchial tree.

For severely exposed casualties, the initial dose of atropine should be at least the 6 mg from the three autoinjectors. 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 IV 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 may 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 the 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 or ATNAAs are administered together to a severely poisoned casualty, diazepam should be administered with the contents of the third Mark I or ATNAA, whether or not there are indications of seizure activity. The risk of respiratory depression from this amount of diazepam given intramuscularly is negligible.

Hypotension 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 result in elevation of the blood pressure 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. After respiration is at least partly spontaneous, secretions are minimized, and the casualty is partly alert, continued 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 greater than 90% of its baseline value and that the individual is otherwise symptom-free 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 or ATNAA) 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 mission-oriented, protective posture, level 4 gear should protect against further exposure. The soldier should be returned to active duty if able and needed.

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 hours to several days following exposure, 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,[18,45] and these factors must be considered before returning a soldier to duty. 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.[88]

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.[45]

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 the soldier's visual acuity compared with the visual demands of the job, and 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.

In the Iran-Iraq War, Foroutan[12] claims to have recommended to commanders that units who had come under nerve agent attack be held back from the front lines for a period of time until they had reconstituted their ChE. It is not clear whether the commanders followed his recommendation. This is the only instance known of a unit-level recommendation on a group of soldiers exposed to nerve agent. US doctrine is silent on this subject. In the planning for the 2003 invasion of Iraq, the authors were told that the theater surgeon responded to the issue, saying the commander on the ground would evaluate each situation as it presented itself.

TREATMENT GUIDELINES IN CHILDREN

Very little has been published on the treatment of nerve agent poisoning in the pediatric population. Rotenberg and Newmark have summarized the literature and extrapolated treatment guidelines based upon adult experience and animal data.[217]

In general, children are more susceptible to chemical agents than adults, based on the following: smaller mass and higher surface-to-volume ratio; immaturity of the respiratory system; immaturity of the stratum corneum in the skin of young children, which facilitates dermal absorption; and immaturity of the neurotransmitter systems, rendering children more likely to seize with an epileptogenic stimulus. In addition, the signs and symptoms of nerve agents in children may well differ from those seen in adults; miosis is less common in organophosphate poisonings in children than in adults, and children may present with less obvious convulsions/seizures than adults.

To treat children exposed to nerve agents, the authors recommend an atropine dose of at least 0.05 mg/kg IM or IV, with a higher dose of up to 0.1 mg/kg in a clear cholinergic crisis. Although technically off-label, the MARK 1 autoinjectors are probably safe to use in children who are large enough for the autoinjector needles. The FDA has approved 0.5 mg and 1 mg autoinjectors of atropine only, representing 25% and 50% of the adult (MARK 1/ATNAA) dose, with correspondingly shorter needles. For 2-PAM Cl, IV use is preferred in small children, and doses might not need to be repeated as frequently as in adults because the half-life of the drug in children appears to be twice that seen in adults. The treatment of seizures in children is similar to those in adults, with benzodiazepine dose adjusted for weight, as long as the caregiver remembers that status epilepticus may present differently in children than adults.

LESSONS FROM IRAN, JAPAN, AND IRAQ

With the exception of two soldiers exposed to sarin in Baghdad, Iraq in May 2004, the United States military has no experience with treating nerve agent casualties on the battlefield. Until then, the entire national experience had been with industrial accidents, many of which have already been described. In order to properly plan for either battlefield or terrorist incidents, it is crucial to learn from those who have dealt with these scenarios. The only appropriate experience comes from overseas, from the Iranian experience with battlefield nerve agent casualties in the Iran-Iraq War and from the Japanese experience with the 1994 and 1995 terrorist attacks.

Iran

From the 1930s until the 1981–1987 Iran-Iraq War, nerve agents were not used on the battlefield. Between 1984 and 1987, Iraq used tabun and sarin extensively against Iranian troops. Only in the last few years has good clinical data emerged from that experience. Foroutan, the first physician to run a chemical treatment station treating nerve agent battlefield casualties in world history, published his

reminiscence of nerve agent and sulfur mustard casualty care in a series of articles in the Farsi-language *Kowsar Medical Journal* in the late 1990s.[218–227] The lessons Foroutan learned have been summarized in an English-language review paper.[12] Among the conclusions this analysis reached, Foroutan determined the differential diagnosis included cyanide poisoning, heat stroke, infectious diseases, fatigue, and psychiatric diagnoses, including combat s tress. At the time, the Iranians thought Iraq had also used cyanide, but that was never proven.

Foroutan used large amounts of atropine in his treatment protocols. This may have resulted from the lack of oxime therapy far forward; Iranian soldiers did not carry oxime with them, and even physicians had a very small supply to use. It may also have been due to Foroutan's inability to guarantee that atropine would be given during medical evacuation to the rear of his location. In a few cases, Foroutan actually gave 200 mg of atropine IV in a 10-minute to 15-minute period.

Although miosis is a poor guide to atropinization, due to the relative disconnection between the papillary muscle and the circulation, Foroutan noted that the disappearance of miosis or even the appearance of mydriasis was one indication to decrease atropine, "even if the patient's mouth has not completely dried."

Psychogenic casualties, whether those with actual psychiatric diagnoses or simply "worried well," were a major problem for Foroutan, just as they were in the civilian victims of the Tokyo subway attack. He stressed the need to identify them and remove them from the symptomatic patients requiring immediate attention. He also stressed the need to treat patients as quickly as possible in order to achieve optimal outcomes.

Foroutan's experience shows that a robust evacuation and triage system saves lives on the battlefield. In the Hosseiniyeh attack, the one which most overwhelmed his aid station, he received over 300 "severe" patients within 5 hours, along with 1,700 less severely affected patients. One aid station was not equipped to treat all of these patients. This illustrates the need to plan a robust and redundant system that can deal with mass casualties of nerve agent exposure.

Foroutan felt that the numbers of nerve agent casualties had been underestimated by the media and the government of Iran because, unlike sulfur mustard casualties, nerve agent casualties rapidly became well or died. As such, nerve agent survivors had no propaganda value, unlike the photogenic mustard casualties who were evacuated to Europe. He believed that there had been between 45,000 and 100,000 nerve agent casualties in the war, several times the United Nations estimate.

Japan

There is considerable literature on the medical aspects of the two terrorist attacks in Japan, in Matsumoto in 1994 and on the Tokyo subway system in 1995.[53,78,143,165,228–244] One of the major lessons from the Japanese attacks is that 80% of the patients who presented for medical attention were not found to have any signs or symptoms of sarin poisoning. This figure has become a major point in the teaching of mass casualty management of a future nerve agent attack. In Tokyo, for example, the combined figures show about 1,100 of the 5,500 people presenting to medical attention having signs and symptoms of sarin poisoning, ranging from extremely severe to extremely mild. The others could be considered the "worried well."[228] Even those patients who actually did have sarin poisoning symptoms tended to have mild symptoms. For example, at Saint Luke's International Hospital, which saw more patients than any other hospital (641), only 5 patients were deemed "critical."[165,229]

The physicians in the first attack, in the small city of Matsumoto, were able to make the diagnosis of organophosphate poisoning (cholinergic crisis) early by syndromic reasoning. In that part of central Japan insecticide poisoning is common, so the patients could be treated without knowing the specific organophosphate.[230] By contrast, in the later, larger Tokyo attack, diagnosis lagged considerably at many hospitals that were unaccustomed to seeing this condition.

In both the Matsumoto and the Tokyo subway attacks, miosis was the most common symptom.[53,165,229,231,232] Many of the patients had no demonstrated depression of ChE. This reinforces the principle that patients should be treated symptomatically, as laboratory values are not as effective a guide to their conditions as is the clinical examination. At Toranomon Hospital, ChE activity was also found to be a poor guide to the severity of poisoning, based on correlations with clinical picture and other values in 213 patients seen after the Tokyo attack.[233]

Four pregnant women, all with slightly decreased ChE levels, were among the patients evaluated at Saint Luke's International Hospital.[229] They were between 9 and 36 weeks' gestation at the time of poisoning. All delivered healthy infants on schedule and without complications. This may be the only series of pregnant exposed patients ever recorded.

The Japanese experience with acute nerve agent antidotal treatment is highly reassuring because even with delays of diagnosis, the standard protocols using atropine, oximes, and anticonvulsants saved many patients.[229,234,235] Those patients receiving 3 g or more of pralidoxime iodide recovered their ChE levels faster

than those who did not. One peculiarity is that the Japanese oxime is 2-PAM iodide, not 2-PAM Cl, as in the United States. The reason for this is cultural. Japan has a high incidence of thyroid disease and often tries to develop drugs using iodide where possible.[237] Other than that, the Japanese hospital treatment protocols were essentially identical to those described in earlier sections of this chapter, and they were generally effective.

The value of acute therapy was validated in Tokyo. At Saint Luke's, of three patients who presented in full cardiopulmonary arrest, one patient was resuscitated and discharged on hospital day 6.[229] Although in a military situation, like the one described by Foroutan, or in an overwhelming civilian catastrophe, sufficient resources may not be available to give antidotal treatment, the Tokyo case demonstrates that even giving treatment to those who appear to be beyond saving is not necessarily futile.

One of the major lessons learned from the Japanese experience is that healthcare workers in an emergency room, even a well-ventilated one, are at high risk of secondary exposure when patients are neither stripped of their clothing nor decontaminated prior to entry.[236,238] At Keio University Hospital, 13 of 15 doctors in the emergency room reported dim vision, with severe miosis in 8, rhinorrhea in 8, chest tightness or dyspnea in 4, and cough in 2.[234] Six of the 13 received atropine, and one of the 13 received pralidoxime iodide. Despite that, all the doctors continued to practice throughout the day. At Saint Luke's, 23% of the staff reported mild physical disorders, including eye pain, headache, sore throat, dyspnea, nausea, dizziness, and nose pain (based upon a questionnaire in which only 45% of 1063 patients responded).[229]

Another major lesson from the Japanese experience is that, in contrast to many other chemical warfare agents, nerve agent casualties either die or improve in a relatively short period of time. At Saint Luke's, 105 patients were admitted overnight and 95% were discharged within 4 days,[228] indicating that nerve agent mass casualties create an acute, not chronic, problem for the health care system.

Among the most important lessons from the Japanese attacks is that there is the possibility of long-lasting clinical effects from sarin exposure.[236,238–244] Many of these effects overlap with or satisfy criteria for posttraumatic stress disorder and have been chronically disabling for some patients. In one questionnaire study, 60% of responders had symptoms 1, 3, and 6 months after exposure.[239] Many still met posttraumatic stress disorder criteria, and the reported symptoms varied widely, including fear of riding subways, depression, irritation, nightmares, insomnia, and flashbacks.[229] In 85 of 149 patients examined 1 and 2 years after the Matsumoto attack, six had been severely poisoned; of these six patients, four had persistent EEG abnormalities, one reported sensory neuropathies, and one had multifocal premature ventricular contractions. Of 27 moderately poisoned, one had persistent visual field defects.[244] In another series of 18 patients studied 6 to 8 months after exposure, at a time when they were clinically entirely normal, visually evoked responses (P[positive wave]100[milliseconds after the stimulaton]) and sensory evoked responses (P300) were prolonged, although brainstem auditory evoked responses were normal, and some of these patients also had posttraumatic stress disorder at the time.[239] An uncontrolled, 5-year, follow-up questionnaire of Saint Luke's patients suggests many may have developed posttraumatic stress disorder.[78] Within the survivor group, older patients seem to be more susceptible to insomnia.[243]

Iraq

In May 2004 two explosive ordnance soldiers in the US Army came in contact with an old sarin shell, presumably from the Iran-Iraq war, and experienced mild sarin poisoning. The soldiers made the syndromic diagnosis of possible nerve agent exposure themselves. This is noteworthy because no US soldiers had ever had documented nerve agent exposure before. The soldiers experienced miosis, dim vision, increased nasal and oral secretions, and mild dyspnea, and later reported some acute memory disturbances that were not well documented in their medical charts. Their ChEs were estimated by back-calculation to be 39% and 62% reduced from baseline.[245] One of the two soldiers appeared to recover fully but then developed memory difficulties several months later, which may or may not have been due to his documented sarin exposure.[246]

PYRIDOSTIGMINE BROMIDE AS A PRETREATMENT FOR NERVE AGENT POISONING

Aging half time places a significant limitation on oxime antidotal therapy for nerve agents, especially those agents that age rapidly. Aging is the reaction that takes place after ChE has bound to nerve agent, resulting in the loss of a side chain and placing a negative charge on the remaining ChE-agent complex. Oximes, such as 2-PAM Cl, cannot reactivate "aged" enzyme, and thus enzyme that has been bound to nerve agent and subsequently aged must be replaced by new synthesis of ChE by the body. Most nerve agents

TABLE 5-8

AGING HALF-TIME OF NERVE AGENTS

Nerve Agent	RBC-ChE Source	Aging Half-Time
GA (tabun)	Human (in vitro)	>14 h[1]
	Human (in vitro)	13.3 h[2]
GB (sarin)	Human (in vivo)	5 h[3]
	Human (in vitro)	3 h[1]
GD (soman)	Marmoset (in vivo)	1.0 min[4]
	Guinea pig (in vivo)	7.5 min[4]
	Rat (in vivo)	8.6 min[4]
	Human (in vitro)	2–6 min[1]
GF	Human (in vitro)	40 h[1]
	Human (in vitro)	7.5 h[5]
VX	Human (in vitro)	48 h[3]

RBC-ChE: red blood cell cholinesterase

(1) Mager PP. *Multidimensional Pharmacochemistry*. San Diego, Calif: Academic Press; 1984: 52–53. (2) Doctor BP, Blick DW, Caranto G, et al. Cholinesterases as scavengers for organophosphorus compounds: Protection of primate performance against soman toxicity. *Chem Biol Interact*. 1993;87:285–293. (3) Sidell FR, Groff WA. The reactivatibility of cholinesterase inhibited by VX and sarin in man. *Toxicol Appl Pharm*. 1974;27:241–252. (4) Talbot BG, Anderson DR, Harris LW, Yarbrough LW, Lennox WJ. A comparison of in vivo and in vitro rates of aging of soman-inhibited erythrocyte acetylcholinesterase in different animal species. *Drug Chem Toxicol*. 1988;11:289–305. (5) Hill DL, Thomas NC. *Reactivation by 2-PAM Cl of Human Red Blood Cell Cholinesterase Poisoned in vitro by Cyclohexylmethylphosphonofluoridate (GF)*. Edgewood Arsenal, Md: Medical Research Laboratory; 1969. Edgewood Arsenal Technical Report 43-13.

age slowly enough that this limitation is not crucial either tactically or clinically (Table 5-8). For example, although VX is extremely toxic, it ages so slowly that in any clinically relevant time frame, oxime will still be useful. The concern, however, has always centered upon rapid-aging nerve agents such as soman, whose aging half-time is on the order of minutes. Once several half-times have elapsed, oxime therapy is useless in a patient poisoned by such a nerve agent.

Due to the limitations of existing therapy, the US and other militaries turned to the carbamates. Pyridostigmine is one of the best known drugs of this class. Its chemical structure and that of a related carbamate, physostigmine, are shown in Figure 5-9. Physostigmine acts similarly, but because it crosses the blood-brain barrier, there is the possibility of behavioral side effects and it is therefore not used as a nerve agent pretreatment. Like the nerve agents, carbamates inhibit the enzymatic activity of AChE. As a quaternary amine, pyridostigmine is ionized under normal physiological conditions and penetrates poorly into the CNS. Pyridostigmine has been approved by the FDA since 1952 for the treatment of myasthenia gravis. In myasthenic patients, pyridostigmine prolongs the activity of ACh. Dosage of pyridostigmine for myasthenic patients in the United States starts at 60 mg by mouth every 8 hours and increases from there; patients receiving 480 mg per day are not unusual. Consequently, pyridostigmine has a long and favorable safety record in this patient population.

As an inhibitor of AChE, pyridostigmine in large doses mimics the peripheral toxic effects of the organophosphate nerve agents. It may seem paradoxical that carbamate compounds protect against nerve agent poisoning, but two critical characteristics of the carbamate-enzyme bond contribute to the usefulness of carbamates for this purpose. First, carbamoylation, the interaction between carbamates and the active site of AChE, is freely and spontaneously reversible, unlike the normally irreversible inhibition of AChE by the nerve agents. No oxime reactivators are needed to dissociate, or decarbamoylate, the enzyme from a carbamate compound. Carbamates do not undergo the aging reaction of nerve agents bound to AChE. The second characteristic is that carbamoylated AChE is fully protected from attack by nerve agents because the active site of the carbamoylated enzyme is not acces-

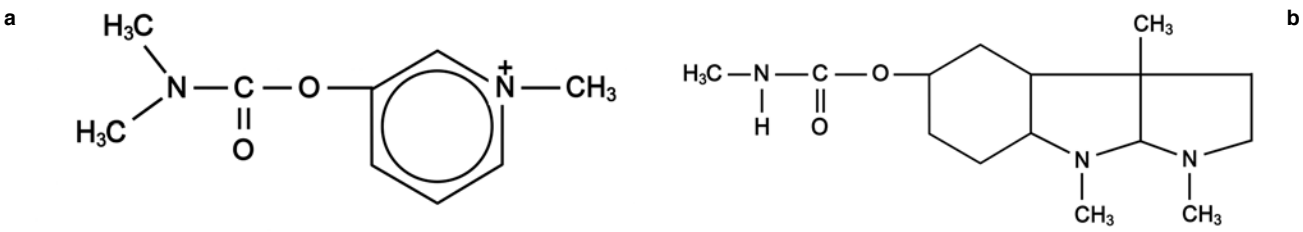

Fig. 5-9. The chemical structures of the carbamates **(a)** pyridostigmine and **(b)** physostigmine.

sible for binding nerve agent molecules. Functionally, sufficient excess AChE activity is normally present in synapses so that carbamoylation of 20% to 40% of the enzyme with pyridostigmine does not significantly impair neurotransmission.

Additionally, it must be recognized that the normal human carries excess ChE. Thus, temporary inhibition of a small portion of ChE is well tolerated by humans, with minimal side effect profiles, as detailed below.

When animals are challenged with a lethal dose of nerve agent, AChE activity normally decreases rapidly, becoming too low to measure. In pyridostigmine-pretreated animals with a sufficient quantity of protected, carbamoylated enzyme, spontaneous decarbamoylation of the enzyme regenerates enough AChE activity to sustain vital functions, such as neuromuscular transmission to support respiration. Prompt postexposure administration of atropine is still needed to antagonize ACh excess, and an oxime reactivator must also be administered if an excess of nerve agent remains to attack the newly uncovered AChE active sites that were protected by pyridostigmine.

TABLE 5-9

EFFECT OF THERAPY ON MEDIAN LETHAL DOSE IN MONKEYS EXPOSED TO SOMAN

Group	Mean LD_{50} (μg/kg) [95% CL]	Mean Protective Ratio [95% CL]
Control (no treatment)	15.3 [13.7–17.1]	NA
Postexposure atropine + 2-PAM Cl	25.1 [22.0–28.8]	1.64 [1.38–19.5]
Pyridostigmine pretreatment + postexposure atropine + 2-PAM Cl	> 617	> 40*

*Indeterminate because of small number of subjects; PR relative to the atropine plus 2-PAM Cl group > 24 (617 ÷ 25.1)
2-PAM Cl: 2-pyridine aldoxime methyl chloride
CL: confidence limit (based on a separate slopes model)
LD_{50}: median lethal dose
NA: not applicable
PR: factor by which the LD_{50} of a nerve agent challenge is raised (in this experiment, the LD_{50} for group given therapy divided by the LD_{50} for control group)
Adapted from: Kluwe WM. Efficacy of pyridostigmine against 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 of Chemical Defense; 1987: 233.

Efficacy

Because it is impossible to test the rationale in humans exposed to nerve agents, the US military embarked upon a series of studies in animal models. Table 5-9 summarizes one study using male rhesus monkeys.[73] Pretreatment with orally administered, pyridostigmine-inhibited circulating red blood cell AChE (RBC-AChE) by 20% to 45%. (Inhibition of RBC-AChE by pyridostigmine is a useful index of its inhibition of AChE in peripheral synapses). Monkeys that had no pyridostigmine pretreatment were not well protected from soman by the prompt administration of atropine and 2-PAM Cl. The PR of 1.64 in these monkeys is typical of the most effective known postexposure antidote therapy in animals not given pretreatment to a soman challenge. In contrast to this low level of protection, however, the combination of pyridostigmine pretreatment and prompt postchallenge administration of atropine and 2-PAM Cl resulted in greatly improved protection (PR > 40 when compared with the control group; PR = 24 when compared with the group given atropine and 2-PAM Cl).

Because the number of animals available for soman challenge at extremely high doses was limited, accurate calculation of a PR was indeterminate in this experiment. The PR was well in excess of 40, clearly meeting the requirement for effectiveness of 5-fold improved protection. In a later study, four of five rhesus monkeys receiving pyridostigmine pretreatment and postexposure therapy of atropine and 2-PAM Cl survived for 48 hours after being challenged with GF at a level 5-fold higher than its LD_{50}.[247]

Pyridostigmine pretreatment shows its strongest benefit, compared with atropine and oxime therapy alone, in animals challenged with soman and tabun, and provides little additional benefit against challenge by sarin or VX.[248–250] Table 5-10 shows the PRs obtained in animals given atropine and oxime therapy after challenge with the five nerve agents with and without pyridostigmine pretreatment. As shown, pyridostigmine pretreatment is essential for improved survival after soman and tabun challenge. With sarin or VX, depending on the animal system studied, pyridostigmine causes either no change or a minor decrease in PRs, which still indicate strong efficacy of atropine and oxime therapy for exposure to these agents. The data for GF show no benefit from pyridostigmine pretreatment for mice and a small benefit for guinea pigs. The only published data on protection of primates from GF show a PR of more than 5 with pyridostigmine pretreatment and atropine/oxime therapy, but a control group treated with atropine/oxime alone

TABLE 5-10

EFFECT OF THERAPY WITH AND WITHOUT PYRIDOSTIGMINE PRETREATMENT ON PROTECTIVE RATIOS IN ANIMALS EXPOSED TO NERVE AGENTS

		Protective Ratio	
Nerve Agent	**Animal Tested**	**Atropine + Oxime**	**Pyridostigmine + Atropine + Oxime**
GA (Tabun)	Rabbit[1]	2.4	3.9
	Mouse[2]	1.3	1.7/2.1*
	Guinea pig[2]	4.4	7.8/12.1*
	Rabbit[3]	4.2	> 8.5
GB (Sarin)	Mouse[2]	2.1	2.2/2.0*
	Guinea pig[2]	36.4	34.9/23.8*
GD (Soman)	Mouse[4]	1.1	2.5
	Rat[5]	1.2	1.4
	Guinea pig[6]	1.5	6.4/5.0*
	Guinea pig[7]	2.0	2.7/7.1*
	Guinea pig[8]	1.9	4.9
	Guinea pig[9]	1.7	6.8
	Rabbit[1]	1.4	1.5
	Rabbit[4]	2.2	3.1
	Rabbit[3]	1.9	2.8
	Rhesus monkey[10]	1.6	> 40
GF	Mouse[11]	1.4	1.4
	Guinea pig[11]	2.7	3.4
	Rhesus monkey[12]		> 5
VX	Mouse[2]	7.8	6.0/3.9*
	Rat[5]	2.5	2.1
	Guinea pig[2]	58.8	47.1/45.3*

*Two doses of pyridostigmine were used.

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for comparison was not included.[247] Clinical experts from all countries have concluded from these data that pyridostigmine isan essential pretreatment adjunct for nerve agent threats under combat conditions, where the identity of threat agents is uncertain.

The effectiveness of pyridostigmine pretreatment may not provide conclusive evidence of the importance of central mechanisms in respiratory arrest; it appears that there is at least partial permeability of the blood-brain barrier to polar compounds such as pyridostigmine, specifically in the regions of the fourth ventricle and brainstem, where respiratory centers are located. In addition, an increase in blood-brain barrier permeability occurs rapidly after soman administration.[251,252] The key observation remains that animals pretreated with pyridostigmine and promptly receive atropine and oxime therapy after an otherwise lethal soman exposure are able to maintain adequate respiration and survive.

Safety

Pyridostigmine maintains a good safety record following its administration to myasthenia gravis patients. Known adverse reactions have been limited to infrequent drug rashes after oral administration and the constellation of signs of peripheral cholinergic excess, which have been seen only when the dosage in patients with myasthenia gravis was increased to AChE inhibition levels well beyond the 20% to 40% range desired for nerve agent pretreatment. The recommended dose for nerve agent pretreatment, based upon non-human primate studies and human pharmacokinetic studies, is only half of the starting myasthenic dose of 60 mg orally every 8 hours, 30 mg orally every 8 hours. When this recommended adult dose regimen has been followed, no significant decrements have been found in the performance of a variety of military tasks. A review of British studies reported that pyridostigmine caused no changes in memory, manual dexterity, vigilance, day and night driving ability, or in psychological tests for cognitive and psychomotor skills.[253] No significant changes in sensory, motor, or cognitive functioning at ground level, at 800 ft, and at 13,000 ft were noted in 12 subjects in another study after their fourth 30-mg dose of pyridostigmine.[254]

The flight performance of subjects taking pyridostigmine in two studies was not affected,[255,256] and no impairment in neuromuscular function was noted in another study in which subjects took pyridostigmine for 8 days.[257] Cardiovascular and pulmonary function were normal at high altitudes in pyridostigmine -treated subjects in another study.[258] However, one study noted a slight decrement in performance in subjects taking pyridostigmine when they performed two tasks simultaneously; these subjects also had a slight decrement on a visual probability monitoring task.[259] Two studies found an increase in sweating and a decrease in skin blood flow in pyridostigmine-treated subjects subjected to heat/work stress.[260,261]

Although there has been wide experience with long-term administration of pyridostigmine to patients with myasthenia gravis, until recently, there was no comparable body of safety data in healthy young adults. Short-term pyridostigmine administration (on or two doses of 30 mg each) has been conducted in peacetime in some countries, including the United States, to screen critical personnel, such as aircrew, for unusual or idiosyncratic reactions, such as drug rash. The occurrence of such reactions has been well below the 0.1% level. Currently no military populations are routinely screened with administration of a test dose of pyridostigmine.

A limited number of animal studies of toxicological abnormalities and teratogenicity and mutagenicity in animals that were given pyridostigmine have had negative results (Hoffman-LaRoche, proprietary information).[262] In a study[263] in which pyridostigmine was administered to rats, either acutely or chronically, in doses sufficient to cause an average 60% AChE inhibition, ultrastructural alteration of a portion of the presynaptic mitochondria at the neuromuscular junction resulted, as well as alterations of nerve terminal branches, postsynaptic mitochondria, and sarcomeres. These morphological findings, which occurred at twice the AChE inhibition level desired in humans, have not been correlated with any evidence of functional impairment at lower doses, but they emphasize the need to limit enzyme inhibition to the target range of 20% to 40%. Pyridostigmine has been used by pregnant women with myasthenia gravis at higher doses and for much longer periods than it was used during the Persian Gulf War and has not been linked to fetal malformations.[264] Because safety in pregnancy has not been completely established, the FDA considers pyridostigmine a Class C drug (ie, the risk cannot be ruled out).

Several studies have sought information on pyridostigmine use under certain conditions: soldiers in combat who frequently take other medications; wounding and blood loss; and use while undergoing anesthesia. The possible interaction of pyridostigmine with other commonly used battlefield medications was reviewed by Keeler.[265] There appears to be no pharmacological basis for expecting adverse interactions between pyridostigmine and commonly used antibiotics, anesthetics, and analgesic agents. In a study[266] of pyridostigmine-treated swine, for example, the autonomic circulatory responses to hemorrhagic shock and resuscitation appeared normal. One potentially

important effect of pyridostigmine deserves consideration by field anesthesiologists and anesthetists using muscle relaxants for anesthesia induction: depending on the duration of muscle-relaxant administration, there may be either up- or down-regulation of postsynaptic ACh receptors.[265] Clinical assessment of the status of neuromuscular transmission using a peripheral nerve stimulator should provide a basis for adjusting the dose of both depolarizing and nondepolarizing muscle relaxants to avoid an undesirable duration of muscle paralysis.

Wartime Use

Pyridostigmine was used to protect soldiers from an actual nerve agent threat in the Persian Gulf War. United States and Allied decisions to use pyridostigmine followed established doctrine, taking into account Iraqi capabilities and intentions. Iraq was known to have substantial stocks of sarin and VX, for which pyridostigmine pretreatment is unnecessary. However, Iraq was also known to be interested in acquiring any compounds that might defeat Allied protection, such as the rapidly aging nerve agent, soman. The security of Warsaw Pact stocks of soman, for example, was a growing concern in 1990.

It was also known in 1990 that Iraq had begun large-scale production of GF, a laboratory compound that had not earlier been manufactured in weapons quantity. International restrictions on the purchase of chemical precursors of the better-known nerve agents may have led Iraq to acquire cyclohexyl alcohol, which it was then able to use to produce GF. Very limited data on medical protection against GF were not reassuring. Although GF's aging time with AChE was reported to be relatively long (see Table 5-8), unpublished information from Allied countries suggested that postexposure atropine/oxime therapy in rodents exposed to GF did not protect against the effects of GF poisoning. As confirmed by the later studies shown in Table 5-10, atropine/oxime therapy only provided rodents with PRs in the range of 1.4 to 2.7. The only primate data available showed that rhesus monkeys given pyridostigmine pretreatment and atropine/oxime therapy uniformly survived a 5-LD_{50} challenge with GF.[246] Concern about Iraq's new GF capability, added to its known interest in acquiring soman, made Allied use of pyridostigmine a reasonable course of action.

Pyridostigmine bromide tablets, 30 mg, to be taken every 8 hours, are currently maintained in stocks of US combat units. The compound is packaged in a 21-tablet blister pack called the "nerve agent pyridostigmine pretreatment set," or NAPPS). One nerve agent pyridostigmine treatment set packet provides a week of pyridostigmine pretreatment for one soldier.[182,183]

The decision to begin pretreatment with pyridostigmine is made by commanders at Army division level or the equivalent, based on assessment of the nerve agent threat by their chemical, intelligence, and medical staff officers.[182,183,266] Because of the lack of data on long-term administration of pyridostigmine to healthy adults, current doctrine calls for a maximum pretreatment period of 21 days, with reassessment at frequent intervals of the need for continued pretreatment. A commander may extend the period once, but requires the approval of the first general or flag officer in the chain of command.

Pyridostigmine is poorly absorbed when taken orally; its bioavailability is 5% to 10%.[267] Ideally, two doses of pyridostigmine, taken 8 hours apart, should be administered prior to any risk of nerve agent exposure.[182,183,266] However, some benefit would be expected even if the first pyridostigmine dose is taken an hour before nerve agent exposure. Because excessive AChE inhibition can impair performance, no more than one 30-mg tablet should be taken every 8 hours. If a dose is forgotten or delayed, administration should simply be resumed on an 8-hour schedule as soon as possible, without making up missed doses.

In Operation Desert Storm in 1991, pyridostigmine was administered under combat conditions for the first time to US and Allied soldiers thought to be at risk for nerve agent exposure. Data on safety and possible adverse responses were collected from the unit medical officers caring for the 41,650 soldiers of the XVIII Airborne Corps, who took from 1 to 21 doses of pyridostigmine during January 1991.[268] Most major unit commanders continued the medication for 6 to 7 days, with over 34,000 soldiers taking it for that duration. They were able to perform their missions without any noticeable impairment, similar to findings with peacetime volunteers participating in studies.[253] However, they reported a higher-than- expected incidence of side effects, as noted in Table 5-11.

Gastrointestinal changes included flatus, loose stools, and abdominal cramps that were noticeable but not disabling. These side effects, together with urinary urgency, were of sufficient intensity for many soldiers to associate them with the medication. In most soldiers, these changes were noticed within hours of taking the first tablet. In many, the effects subsided after a day or two of administration, and in others they persisted as long as pyridostigmine was administered. Some units adopted a routine of taking pyridostigmine with meals, which was thought to minimize gastrointestinal symptoms.

Soldiers taking pyridostigmine during this period

TABLE 5-11

EFFECTS OF PYRIDOSTIGMINE PRETREATMENT* ON US SOLDIERS IN THE PERSIAN GULF WAR

Effect	Incidence (%) N=41,650
Gastrointestinal symptoms	≤50
Urinary urgency and frequency	5–30
Headaches, rhinorrhea, diaphoresis, tingling of extremities	< 5
Need for medical visit	< 1
Discontinuation on medical advice	< 0.1

*Dose was 30 mg pyridostigmine bromide, administered orally every 8 hours for 1 to 7 days.
Adapted with permission from: Keeler JR, Hurst CG, Dunn MA. Pyridostigmine used as a nerve agent pretreatment under wartime conditions. *JAMA*. 1991;266:694.

were also experiencing a wide range of other wartime-related stresses, such as repeatedly donning and removing their chemical protective suits and masks in response to alarms, sleep deprivation, and anticipation of actual combat. Because there was no comparable group of soldiers undergoing identical stresses but not administered pyridostigmine, it is not clear to what extent pyridostigmine itself was responsible for the symptoms noted above. The findings are thus a worst-case estimate for effects attributable to pyridostigmine use in wartime.

Among these soldiers, less than 1% sought medical attention for symptoms possibly related to pyridostigmine administration (483 clinic visits). Most of these had gastrointestinal or urinary disturbances. Two soldiers had drug rashes; one of them had urticaria and skin edema that responded to diphenhydramine. Three soldiers had exacerbations of bronchospasm that responded to bronchodilator therapy. Because the units of the XVIII Airborne Corps had been deployed to a desert environment for 5 months before pyridostigmine was used, most soldiers with significant reactive airways disease had already developed symptoms and had been evacuated earlier. The consensus among medical personnel more recently arrived was that they saw more pyridostigmine-related bronchospasm in their soldiers who had not been present in theater as long. Later, many soldiers said that they simply stopped taking the medication and did not report symptoms to their medical officers.[269]

Because of increased exposure to the work-of-breathing requirements of being masked, as well as inhaled dust, smoke, and particles, it was unclear whether pyridostigmine was a major causative factor in those who had bronchospasm at the onset of hostilities. Two soldiers from the XVIII Airborne Corps had significant blood pressure elevations, with diastolic pressures of 110 to 120 mm Hg, that manifested as epistaxis or persistent bleeding after a cut and subsided when pyridostigmine was stopped. Another soldier who took two pyridostigmine tablets together to make up a missed dose experienced mild cholinergic symptoms, self-administered an atropine autoinjector, and recovered fully after several hours. There were no hospitalizations or medical evacuations attributable to pyridostigmine among XVIII Airborne Corps soldiers. In other units, at least two female soldiers, both weighing approximately 45 to 50 kg, noted increased salivation, muscular twitching, severe abdominal cramps, and sweating that prompted medical observation. The symptoms subsided after pyridostigmine was stopped. This experience suggests that cholinergic symptoms may occur in a small number of individuals with relatively low body weight.

In a group of 213 soldiers in Israel who took pyridostigmine (30 mg every 8 h), 75% reported at least one symptom.[270] Included among these symptoms were excessive sweating (9%), nausea (22.1%), abdominal pain (20.4%), diarrhea (6.1%), and urinary frequency (11.3%). In a smaller group of 21 soldiers, pseudocholinesterase (also called butyrocholinesterase, which is discussed later in this chapter) activity was the same in the 12 who were symptomatic and the 9 who were not symptomatic.[40]

An Israeli soldier who developed cholinergic symptoms after taking pyridostigmine was reported to have a genetic variant of serum butyrlcholinesterase.[271] The variant enzyme has low binding affinity for pyridostigmine and other carbamates. The authors of the report suggested that people who are homozygous for the variant enzyme could therefore show exaggerated responses to anticholinesterase compounds. The soldier had a history of prolonged apnea after receiving succinylcholine premedication for surgery. People with similar histories of severe adverse responses to cholinergic medications should be carefully assessed concerning their potential deployability to combat, where they might face either a nerve agent threat or the potential need for resuscitative surgery involving emergency induction of anesthesia[265] using cholinergic medications.

Because pyridostigmine was used during the Persian Gulf War and troops were ordered to take it, and because some returning troops have reported unexplained medical symptoms, the possible role

of pyridostigmine in the genesis of these problems has been questioned. A full discussion of this issue lies beyond the scope of this volume. Some studies performed since the Gulf War give reassurance that pyridostigmine used as called for in military doctrine does not by itself give rise to lasting neuromuscular problems such as fatigue, probably the most commonly related complaint. In one human study, a retrospective analysis showed that handgrip strength was not associated with pyridostigmine intake (P = 0.558).[272] In another study using animal muscle cells in culture, ultrastructural alterations seen by electron microscopy after 2 weeks of exposure to low-dose pyridostigmine were reversible following withdrawal of the drug.[273]

On the other hand, a more worrisome concern about pyridostigmine in a battlefield context is the situation in which a soldier who has been on the drug in accordance with pretreatment doctrine needs surgery acutely. Because pyridostigmine is a ChE inhibitor, one might expect that recovery from anesthesia using a neuromuscular blocking agent, such as succinylcholine, would be prolonged, and according to a prospective human study, such is the case.[274] This is of particular concern in those rare patients with mutant BuChE, as mentioned above.[271] Anesthesia providers in a combat zone must anticipate increased time to recovery of normal function, including that of the muscles of respiration, in troops on pyridostigmine, but the magnitude of the increase does not imply that this should affect the decision to go to surgery using these anesthetic agents.

It is now clear that pyridostigmine can be used effectively in large military populations under combat conditions without impairing mission performance. On the other hand, soldiers must have a clear understanding of the threat and the need for this medication. Otherwise, it seems unlikely that they will be willing to accept the associated gastrointestinal and urinary symptoms or to comply with an 8-hour dosage schedule.

Regulatory Status

Before the 1990 Persian Gulf War, the regulatory status of pyridostigmine for nerve agent pretreatment was as an off-label use of an approved medication. Additionally, the 30 mg dose was not approved, since the only on-label indication was for myasthenia gravis and the smallest adult dose was 60 mg. Because of the impending war, in 1991 the FDA waived informed consent for its use to make the best medical treatment available in a specific combat situation.[275,276] The FDA based this waiver on two factors. First, it relied on data from animal studies conducted in both the United States and other NATO countries that found that pyridostigmine increases survival when used as pretreatment against challenge by certain nerve agents (data on efficacy in humans challenged by nerve agents is not experimentally obtained). Second, it determined a long history of safety when the drug was used for approved indications at doses several-fold higher than the doses administered in the military.

The waiver of informed consent was withdrawn in 1992. From then until 2003, the status of pyridostigmine used for nerve agent pretreatment was that of an investigational new drug. This status resulted in the Department of Defense creating an informed consent protocol should the need again arise to order troops to take it. At no time was it illegal for a licensed physician to prescribe pyridostigmine to a patient, whether military or not, wishing to use the drug for this purpose.

In February 2003, on the eve of the invasion of Iraq, the FDA approved pyridostigmine as a nerve agent pretreatment for soman only. This was the first time the FDA applied the "animal rule" to approve a medication for use against chemical or biological warfare agents without Phase 2 and Phase 3 human clinical trial data. Technically, no other nerve agent is covered by this approval. Realistically, however, from a tactical standpoint, knowledge of the specific agent may not be available when a commander must decide whether or not to order troops to take it. Pyridostigmine is not suited for any population group not in imminent danger of exposure to a rapidly aging nerve agent. Despite increased concerns about chemical terrorism, no first-responder agency in the United States has seriously considered ordering responders to take pyridostigmine.

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, hyperac-

tivity 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 ACh at muscarinic but not nicotinic receptors, the oxime 2-PAM Cl, which breaks the agent-enzyme bond formed by most agents, and anticonvulsant treatment with diazepam or other benzodiazepines in cases of severe poisoning. Assisted ventilation and other supportive measures are also required in severe poisoning.

For proper protection, it may be necessary to pretreat those at high risk of exposure to a rapidly aging nerve agent, such as soman, with pyridostigmine, a carbamate that reversibly binds a fraction of the body's ChE. This medication now carries FDA approval against soman only.

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