Nerve Gases

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Nerve gases are organophosphorus chemical warfare agents that cause irreversible inhibition of acetylcholinesterase and are capable of causing death within minutes, due to respiratory failure, cardiovascular collapse, and epileptiform seizures. Although successful treatment is possible for exposure at or near lethal concentrations, treatments are hazardous and ineffective after a massive exposure. Residual symptoms and electroencephalographic abnormalities may persist for a year or more after exposure to small amounts of these agents or successful treatment of a larger exposure. Protective clothing and masks are effective, but limit mobility and vision and produce adverse psychological reactions during combat training exercises. The psychological reactions to chemical warfare defenses may be mistaken for the effects of the agents themselves and lead to inappropriate treatment or possible inadvertent escalation of hostilities. Although the United States and the Soviet Union are committed to the destruction of aging chemical weapons and the negotiation of new treaties to limit or ban their use, proliferation and terrorist actions remain as a source of legitimate concern. More effective international controls are needed. [PSRQ 1991;7:69–76]

War in the Middle East and confirmed reports that in the past Iraq has used chemical weapons in the form of the vesicant, mustard gas, and the nerve gas, tabun [1,2], in addition to reports that the Libyans built a large chemical plant with the putative potential for producing chemical weapons, have heightened fears that these agents might be used during battle or by terrorists. This review examines the current status of nerve gas weapons

Nerve gas is a term typically applied to potent phosphorylating agents that irreversibly bind to the esteric subsite of acetylcholinesterase (AChE) resulting in permanent inactivation of this enzyme. The high stability of the phosphorylated enzyme is fur-

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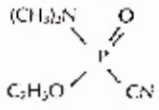
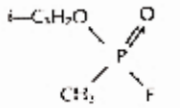
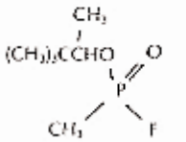
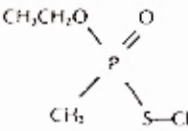
ther increased by "aging" of the phosphorylated enzyme complex; this causes the effect to persist for days or weeks, until new enzyme is synthesized. This severely impairs or prevents all synaptic activity in the central and peripheral nervous systems that uses acetylcholine (ACh) as the neurotransmitter and can result in death or immobilization. The extreme potency and duration of action on AChE, rapidity of action, difficulties in treatment of exposure to these agents, combined with their long-term stability during storage, and ease of dissemination, have led to the production of certain of these compounds as agents to be used in warfare. The initial compound found to have antiacetylcholinesterase (anti-AChE) activity was physostigmine, also known as eserine. This alkaloid is obtained from the Calabar or "ordeal" bean (Physostigma venenosum), which was used by tribes in West Africa in trials for witchcraft, and later saw clinical use in 1877 for the treatment of glaucoma [3,4]. Subsequent research into the nature of drugs with anti-AChE activity led to the definition of the structural requirements for anti-AChE activity and to the development of agents with extreme toxicity for use as chemical warfare agents, including sarin, soman, tabun, and VX (Table 1) as well as a variety of widely used pesticides such as malathion and dimpylate (Diazinon).

Table 1

General formula for organophosphates with anticholinesterase activity. R_1 and R_2 are organic moieties whereas the leaving group, X, in agents with high potency is a halogen, cyanide, or a sulfur-containing group.

Structure	Common name (chemical name)
	Tabun (GA) (Ethyl N-dimethylphosphoramidocyanidate)
	Sarin (GB) (Isopropyl methylphosphonofluoridate)
	Soman (GD) (Pinacolyl methylphosphonofluoridate)
	VX (Methylphosphonothioic acid S-[2-[bis(1-methylethyl)amino] ethyl] O ethyl ester)

MECHANISMS OF ACTION

The effects of anti-AChE agents arise from the failure of AChE (acetylcholine acetylhydrolase, EC 3.1.1.7) to hydrolyze ACh after its release from cholinergic neurons and the accumulation of ACh in locations in the brain, spinal cord, and peripheral sites. In addition to the inactivation of AChE, some anti-AChE agents also act directly on the sites sensitive to acetylcholine (receptors) and mimic its activity. Agents with this property of mimicking ACh are known generically as agonists.

The potent anti-AChE compounds are pentavalent compounds of phosphorous with the general formula shown in Table 1. The two organic radicals modify the reactivity of the compound and have additional effects on the binding of the agent to the enzyme. Initially, the agent forms an agent-enzyme complex in a reversible reaction. A covalent bond is then formed between the drug and the enzyme by the displacement of the leaving group, X. The affinity between the enzyme and the inhibitor is increased further by dealkylation of the drug-enzyme complex, a phenomenon referred to as "aging." For soman, the rate of aging of the inactivated enzyme is equal to the rate at which the pinacoloxyl group is lost and proceeds with a half-time of less than 1.5 minutes [5]. Some reaction kinetics and other properties of tabun, sarin, soman, and VX are shown in Table 2. Although different species exhibit varied sensitivities to these agents, the compounds listed in the table are all extremely potent. Data in the literature conflict concerning the lethal dose for humans, and range from 0.01 mg/kg [6] to higher doses of 100 (sarin) to 400 (tabun) mg·min/M^3 in air [7] which would be equivalent to the inhalation of 1–4 mg of the agent. The lethality of nerve agents depends on the route of administration. Inhalation of vapors (or aerosols) is the most hazardous route. Percutaneous absorption is less hazardous, but lethal amounts can be acquired by this route.

The term nerve "gas" is, in a sense, a misnomer, since the common agents are all liquids at room

Table 2. Some properties of nerve agents

Agent	AChE kinetics in rabbit brain		Human red blood cell AChE inhibition I_{50} (Molar)	Maximum concentration permitted in air (per CDC) (mg/m^3)
	K_d (μM)	k_i (M^{-1} sec^{-1})		
Tabun	6.2	6.8×10^4	2.9×10^{-9}	3×10^{-6}
Sarin	1.7	2.5×10^5	2.5×10^{-9}	3×10^{-6}
Soman	0.3	1.5×10^6	6.3×10^{-10}	
VX	0.9	5.7×10^5		3×10^{-6}

The I_{50} is the molar concentration required to reduce human red cell AChE activity by 50% [3]. K_d is the dissociation constant = k_{-1}/k_1. K_i is the overall inhibitory power = k_2/K_d from the reaction below where EH is the enzyme, IX the inhibitor with its leaving group, X, EH·IH the potentially reversible enzyme-inhibitor complex, and EI, the phosphorylated inhibited enzyme [28].

$$EH + IX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EH \cdot IH \xrightarrow{k_2} EI + HX$$

Maximum permissible levels in air for the population were defined by an open conference at the Centers for Disease Control in September, 1987 [25].

temperature. Chemical weapons delivery systems, therefore, aerosolize these liquids to achieve dispersal. Tabun, sarin, and soman have relatively low vapor pressures and will evaporate and disperse, particularly in hot climates, and are grouped as nonpersistent agents. VX is an oily liquid and may remain unchanged at the dispersal site for weeks or longer, posing a long-term threat, and is classified as a persistent agent.

PHARMACOLOGICAL ACTIONS

The manifestations of poisoning by these agents depend on the route of administration (inhalation, ingestion, or absorption through the skin) and may be localized or generalized. Local effects are generally confined to the eye or respiratory tract, but may be seen in an arm or leg after absorption of the agent through the skin where localized sweating and fine, rapid, and uncoordinated muscular contractions or fasciculations may occur. Agents with anti-AChE activity have the potential to activate and subsequently depress muscarinic ACh receptors in autonomic effector organs and in the brain, as well as nicotinic ACh receptors in autonomic ganglia and skeletal muscle.

Under normal conditions, packets or quanta of ACh are released at a cholinergic synapse when a neural impulse reaches the axon terminal. The ACh diffuses across the synaptic cleft and binds to a postsynaptic site on the target cell, which may be a neuron, muscle, or gland. Subsequent events produce an action potential, muscular contraction, or secretion. The effect is terminated by hydrolysis of the ACh, which is catalyzed by AChE. Inhibition of AChE permits a single molecule of ACh to activate sequential postsynaptic binding sites and leads to a desynchronization of the transmission of neural impulses and persistence of the cholinergic effect. In skeletal muscle, uncoordinated muscular contractions or fibrillations occur and cause weakness. In glands, a massive outpouring of secretions occurs. ACh may also depolarize the presynaptic axon terminal and increase the anti-AChE effect. A state of constant muscular depolarization, or depolarization blockade, may develop when the concentration of ACh at the postsynaptic membrane is sufficiently high. In addition to inactivating AChE, some anti-AChE drugs also act as cholinergic agonists and mimic the action of ACh. The net effect is ineffectual contraction or paralysis of voluntary muscle, including respiratory muscles, leading to immobility and death by asphyxiation, coupled with increases in secretions and airway obstruction.

Miosis, or reduction in the size of the pupil, is the major anti-AChE effect in the eye and is due to a contraction of the pupillary sphincter muscle. The effect is immediate and prolonged. It persisted for 45 days in one worker accidentally exposed to sarin [8]. This miosis promotes the egress of aqueous humor from the anterior chamber, a therapeutic effect that led to the use of physostigmine in the treatment of glaucoma. Increases in the intraocular pressure may occur because of vascular dilatation or an increase in the permeability of the vascular-aqueous humor barrier. In some cases, spasm of the ciliary muscle or engorgement of the ocular vasculature may cause eye pain.

Pulmonary effects are the result of a combination of the profuse production of bronchial secretions and contraction of smooth muscle fibers in bronchioles that may be combined with paralysis of the muscles of respiration. These effects may be the initial symptoms of exposure after inhalation and can lead rapidly to the development of severe hypoxia and death.

In the brain, anti-AChE effects are attributable to mechanisms similar to those encountered at the neuromuscular junction. At low doses or after the acute, life-threatening effects of anti-AChE agents pass, disturbed mentation may persist for long pe-

riods [9–12] With high doses, nervous system depression or epileptiform seizures, or both, occur, which, along with hypoxia, contribute to the cause of death.

In the heart, the excessive accumulation of ACh leads to severe bradycardia and a reduction in cardiac output, further contributing to the cause of death.

TREATMENT

Treatment of anti-AChE intoxication involves the parenteral use of specific pharmacologic agents that act at muscarinic sites to terminate the effects of ACh, such as atropine, parenteral AChE reactivating agents, usually oximes such as pralidoxime, and general supportive measures. These include termination of exposure by the use of masks, protective clothing, and washing; airway maintenance, which may require vigorous endotracheal aspiration, intubation, and artificial ventilation; and the administration of anticonvulsants if seizures occur.

Very large doses of atropine, up to as much as 50 mg/day, may be required to counteract the effects of severe poisoning. To monitor the effects of atropine, an intravenous route is preferable to an intramuscular injection. Atropine should be given until bradycardia has been reversed or copious secretions from the trachea have been stopped, or both.

Reactivation of AChE should be attempted by the infusion of oximes, such as pralidoxime chloride. Pralidoxime is a difficult drug to use, since many of the side effects of the drug cannot be differentiated from those produced by organophosphates. Rapid administration can cause laryngospasm, muscular rigidity, and tachycardia. Individual dose titration is mandatory.

Defenses against nerve agents have been investigated vigorously and reviewed recently [10]. In addition to the treatments discussed above, the military has stockpiled and issued pyridostigmine bromide (a reversible AChE inhibitor) to be taken 30 mg by mouth every 8 hours, in anticipation of an attack, to lower the potential effect of an anti-AChE agent. Benzodiazepine self-injectors are being explored as protection against seizures, and genetic engineering technology is being developed to mass produce AChE to be injected to scavenge anti-AChE agents. Finally, more effective oximes, such as HI-6, are being evaluated [13].

The treatment of organophosphate poisoning is, at best, a difficult complex task associated with a high risk of complications. Pyridostigime must be used with caution in subjects with asthma and may cause adverse reactions that include nausea, vomiting, diarrhea, abdominal cramps, miosis, an increase in bronchial secretions, muscular fasciculation, and weakness. Very high doses can cause an acute cholinergic crisis, respiratory depression, and death These symptoms are due to the stimulation of muscarinic and nicotinic receptors by ACh, and replicate the effects of AChE inhibitors. Benzodiazepines are nervous system depressants that produce drowsiness and an impairment of the level of consciousness that would be likely to cause impaired performance among combatants called on to operate complex equipment or make difficult command decisions The optimism expressed by Dunn and Sidell [10] that research and perfection of defensive measures may lead to "improved medical countermeasures [so that] an enemy capable of a nerve agent attack would not consider it worth trying" seems as unwarranted now as when those sentiments were first expressed in 1950 [14].

LONG-TERM EFFECTS OF EXPOSURE

Although immediate death is the probable outcome of a severe exposure to anti-AChE agents, there are hazards posed to survivors of acute exposures and to those who may be exposed to small doses over long periods of time.

Complaints recorded after accidental exposure include increased dreaming, loss of libido, poor memory, irritability, and poor concentration [12]. A significant number of organophosphates, including sarin, may produce a syndrome of delayed neurotoxicity [15] Humans may be the species most sensitive to this effect. Studies in birds suggest that older individuals are more susceptible than those who are younger After a variable latent period, ataxia appears followed by a flaccid paralysis. Neuropathological studies reveal axonal degeneration that is evident in peripheral nerves as well as the spinocerebellar and corticospinal tracts of the central nervous system. The factors of importance in the production of the syndrome are the nature of the agent, dose, the frequency and duration of exposure, and the route of administration. Rats that survived a single dose of soman or sarin were found

to have brain and myocardial lesions 35 days after exposure [16]. The coexistence of cerebral and cardiac lesions suggested that seizures may be responsible for their pathogenesis. Additional studies of rats exposed to soman or sarin revealed extensive injury to the cortex, hippocampus, amygdala, and thalamus [17]. Again, epileptiform seizures, complicated by ischemia and hypoxia, were suspected as the cause. Direct intracerebral injections of soman or VX causes seizures and neuropathological changes, more marked on the injected side [18]. Pretreatment with atropine prevented the seizures and neuropathological changes, again suggesting a link between seizures and brain injury. However, it is not possible to eliminate completely direct toxic effects of anti-AChE agents since electroencephalographic changes have been observed a year or longer after exposure in monkeys and humans [12] and complaints such as increased dreaming were seen in populations with increased REM sleep.

PSYCHOLOGICAL ASPECTS OF NERVE GAS POISONING

At times when nerve gas attack might occur, the anticipation of an attack might be almost as incapacitating as the attack itself. Although the literature concerning this aspect of the use of these specific agents is sparse, it is likely that the lingering images of gas attacks during World War I and the intangible invisible nature of these colorless, odorless, tasteless agents create a set of subliminal fears. These subliminal fears may be similar to the fears of nuclear attack and radiation, in that they evoke a sense of helplessness, vulnerability, and inevitability of death.

The psychological aspects of chemical warfare have been reviewed from a military perspective by Fullerton and Ursano [9]. A part of the psychological response is probably evoked by the protective clothing required (referred to as Mission Oriented Protective Posture gear, or MOPP). This equipment, referred to elsewhere in the report as an "ensemble," isolates the wearer as completely as possible from the environment and induces claustrophobia in up to 20% of wearers [9]. This equipment is uncomfortable, restricts vision and hearing, and poses hazards to the wearer as the result of heat retention and dehydration that have been responsible for injuries during training exercises, particularly in hot environments or after the consumption of alcohol.

During training exercises, large numbers of the participants report symptoms of varying severity associated with wearing MOPP gear. In 366 individuals these included dyspnea (33% of exercise participants), and reduced peripheral vision (33%), sweating (24%), anxiety (14%–20%), visual disturbances (of unspecified nature) (6%–20%), panic (which may lead to removal of masks, etc.) (1%–10%), auditory hallucinations (7%), and others [9]. The authors suggest that understanding these responses will lead to better training and improved symptom control.

During an actual or anticipated nerve gas attack, group contagion of symptoms may occur. Since many of the symptoms of the psychological reaction to the chemical warfare environment may be indistinguishable from the effects of the agents themselves (difficulty breathing, excessive sweating, fear of dying, etc.), it is likely that errors in diagnosis will be made and inappropriate treatment will be administered. This occurred in Israel after a missile attack in January 1991 [19] when Israelis feared chemical weapon dispersal. Many of the treatments for nerve agent toxicity that are available (atropine) or anticipated (benzodiazepines to prevent seizures) are designed for self-administration. Such errors may cause fatalities or injuries because of the toxicity of the treatments, further impairment of thermoregulation, or symptoms that make subsequent correct diagnosis more difficult.

Finally, orders to initiate defensive measures, such as the use of protective clothing or the administration of pyridostigmine, could be misconstrued by a potential adversary as evidence for an impending attack. This might lead to an unintended escalation of hostilities. Similar concerns have been expressed concerning the activation of civil defense measures in anticipation of a nuclear attack.

CASE REPORTS

In spite of the fact that workers who routinely handle potent anti-AChE agents such as soman and sarin are presumably trained in appropriate procedures, there are reports of as many as 124 individuals accidentally exposed to nerve gas agents [8,9,11,12]. The following accounts, excerpted from the more detailed report by Sidell [11], illustrate the difficulties that may be encountered, even under

optimum circumstances when appropriately trained medical personnel are nearby.

Case 1

A 33-year-old worker at Edgewood Arsenal in Maryland was splashed on the face and in the mouth by less than 1 ml of a 25% (V/V) solution of soman. He washed himself and rinsed his mouth promptly and arrived in the emergency room less than 10 minutes after the exposure. He then collapsed and was comatose with labored respirations. His pupils were 1 or 2 mm in size, the conjuctivae were injected, oral and nasal secretions were profuse, and fasciculations, a contorted facial expression, and neck stiffness were present. Since there was never any doubt about the diagnosis, 2 mg of atropine were given intravenously and a pralidoxime chloride infusion was started within 1 minute. During the next 15 minutes an additional 10 mg of atropine were given, nasal oxygen was administered, and he was suctioned frequently. He became cyanotic, but attempts to insert an endotracheal tube were thwarted by intense facial and jaw muscle contractions. He regained consciousness within 30 minutes but fasciculations persisted for a day. An additional 4 mg of atropine were given intravenously and urinary retention was noted 14 hours after exposure. The next day nausea persisted, atrial fibrillation developed, and he received additional atropine. Prochlorperazine (Compazine), 5 mg, was given intramuscularly twice because of nausea, and caused torticollis and athetosis. These two extrapyramidal side effects were treated with intravenous diphenhydramine hydrochloride. A urinary tract infection, presumably caused by atropine-induced urinary retention and catheterization, further complicated his hospital course.

Psychiatric problems persisted in the form of depression, withdrawal, antisocial thoughts, and poor sleep. These were improved by treatment with scopolamine, an antimuscarinic agent with more pronounced effects on the central nervous system than atropine. He was well 6 months after his exposure.

Case 2

A 52-year-old Edgewood Arsenal employee, wearing full protective gear later found to have a crack in the mask, noted an increase in oral and nasal secretions and difficulty in breathing while cleaning a sarin-contaminated area. Within 5–10 minutes he was in the emergency room, but he had already had an epileptiform seizure and was cyanotic. His breathing was labored, fasciculations of skeletal muscle were present along with miosis, marked salivation, and rhinorrhea. Atropine, 4 mg, was injected and a pralidoxime infusion was started. Twenty minutes later, bronchial secretions increased, additional doses of atropine and pralidoxime were given, and he was intubated and ventilated. Spontaneous ventilations became weaker, vomiting continued, and more atropine and pralidoxime were administered. One hour after exposure he was comatose and apneic.

Two and a half hours after his exposure, still more atropine had been required, but his sensorium had started to clear and spontaneous respirations resumed. By 9 hours, he was able to walk. Electrocardiographic abnormalities were present, and he complained of generalized aches and pains, not thought to characterize cardiac ischemia, but of sufficient concern to warrant continued hospitalization for 4 weeks.

Four months after his exposure he was rehospitalized because of easy fatigability, dyspnea, restlessness, and abdominal and chest pain. He was markedly depressed and anxious with crying spells and restlessness. A psychiatrist attributed this to worry about bodily integrity and his cardiac status. Eighteen months after his exposure he died following a myocardial infarction.

These two cases illustrate the potential difficulties that may be encountered in treating patients with severe anti-AChE poisoning, even in an environment where poisoning might be anticipated and where personnel are trained in appropriate treatment. The first patient had two complications of atropine treatment, urinary retention and a cardiac arrhythmia, in addition to a dystonic reaction to prochlorperazine. It is possible that his laryngospasm and muscular rigidity were caused by pralidoxime and prevented endotracheal intubation. Although no other complications of pralidoxime therapy were noted, these may occur with doses of 5–10 mg/kg [11] and include hypertension, diplopia, blurred vision, nausea and vomiting, respiratory depression, tachycardia, and death, in addition to muscular rigidity and laryngospasm.

For both patients, psychiatric complications due to either the agent itself or the reaction to the ex-

posure persisted long after other manifestations had cleared. There is a high probability that psychiatric symptoms were due to the psychological consequences of a near-death by nerve gas poisoning that acted synergistically with the actual effects of the agents themselves

DISCUSSION

The major nations of the world, horrified by the gas attacks during World War I, signed the Geneva Protocols of 1925 to forbid the first use of chemical and biological weapons. As of 1989, the Protocols had been signed by over 130 nations, with other nations adding their names since then [20]. Although the accords prohibit the initial use of these weapons, they do not prohibit the development, testing, and stockpiling of chemical agents. In 1989, the U.S. stockpile of nerve gas weapons was estimated to be between 22,680 and 27,215 metric tons [21]. The Soviet Union has declared that it has less than 50,000 metric tons of chemical agents [20].

In 1980 the U.S. Congress embarked on an $8 billion program to modernize chemical weapons. This program included appropriations for "binary" weapons, including 115-mm artillery shells (production began in 1987 in Pine Bluff, AR [20]) and "Big Eye" bombs. Binary weapons carry two chemicals in separate containers that mix after firing to form unitary anti-AChEs such as sarin or VX. This program has encountered considerable resistance, particularly in Europe where deployment was considered [22–24]. Further impediments have come from a surprising source: two U.S. based chemical companies have reportedly refused to sell the military the chemicals needed to construct binary weapons [20,25].

In 1985, Congress ordered the destruction of the aging U.S. stockpile of unitary weapons (Public Law 99-145, Department of Defense Authorization Act of 1986). The target date for completion of this task was September 30, 1994, but the law has been amended to delay the realization of that goal by 3 years. As a part of that process, an open meeting was held at the Centers for Disease Control in September of 1987 to review and approve guidelines for exposure and monitoring during disposal [26].

In a recent review of that process, Carnes and Watson [21] reported that community emergency planning for a potential disaster is inadequate and that there is a need to improve communication about risk information, particularly at the eight sites in the U.S. where weapons are stored and where disposal by incineration is intended [21]. Their report is a summary of a comprehensive evaluation of disposal plans [21]. The preparation of the report followed public hearings with input from interest groups such as the Natural Resources Defense Council, and indicates that oversight of final plans will be under the supervision of an agency of the Centers for Disease Control. Carnes and Watson depict several accident scenarios based on 1980 census data and expected gas plume configurations, and describe a "negligible" accident (0–5 fatalities) that might follow the release of up to 5 kg of agent at the Tooele Army Depot in Utah, the repository for 42% of the U.S. chemical weapons stockpile, and a catastrophic accident (more than 1,000 fatalities) that could follow the release of 100–1,000 kg of agent at the Aberdeen Proving Ground in Maryland, which is a repository for mustard gas, or the Blue Grass Army Depot, in Lexington, Kentucky, a repository for mustard gas, sarin, and VX. They conclude, ultimately, that disposal entails less hazard than continued storage.

Following the reaffirmation of the 1925 Protocols at the 1989 Paris Conference on the Prohibition of Chemical Weapons, there have been a number of optimistic statements by both Presidents Bush and Gorbachev concerning the desirability of eliminating chemical weapons [21,25].

Although all of these most recent steps are reassuring, threats of potential nerve agent attacks are likely to persist. These threats are due to concerns about verification of potential treaties, the relative ease with which these agents can be synthesized, and less tangible psychological factors. An enormous increase in these fears would be assured if a terrorist or other verified attack that used nerve agents were to occur.

There are many similarities between the real and imagined consequences of the use of nerve agents and nuclear weapons. Both are appropriately classified as weapons of mass destruction, and research and educational efforts designed to eliminate both have been undertaken [27].

Physicians and other health care professionals have been central in the development of an appropriate awareness of the consequences of nuclear weapons, an effort recognized by the Nobel Com-

mittee in 1985 in its award of the Peace Prize to International Physicians for the Prevention of Nuclear War. Our role in relation to chemical weapons, and nerve agents in particular, is even more clearly defined. Physicists did not develop these weapons—we did.

As health-care workers and scientists it is imperative that we call on the fundamental principle of medicine—do not harm your patient—and refuse to participate in the development of these agents. In addition, careful scrutiny must be exercised in considering what might be legitimate research in the development and testing of defensive and therapeutic measures, as the boundaries between defense and offense are particularly blurred in the case of these weapons. Funding in this area should be removed from the Department of Defense, and supervised as a part of the peer-reviewed program of the National Institutes of Health, National Science Foundation, and similar agencies. Finally, we should continue to urge the U.S. Congress and the United Nations to enact laws and negotiate treaties that include appropriate verification procedures to ban the production and proliferation of chemical (and biological) weapons.

There has been encouraging progress in this direction. In June 1990, the United States and the Soviet Union signed a treaty in which they pledged to cease the production of chemical weapons and to reduce existing stockpiles to "equal, low levels" [28]. The 40-nation Conference on Disarmament in Geneva has been drafting a Chemical Weapons Convention that calls for the complete abolition of all stockpiles of chemical weapons. Determined diplomatic and political efforts will be necessary to resolve the differences between these positions. Physicians can and should be leaders in this endeavor.

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