CHAPTER 2

NERVE AGENTS

SECTION I - GENERAL

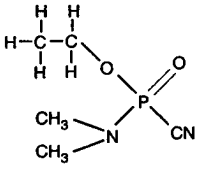
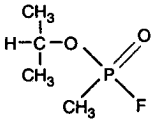
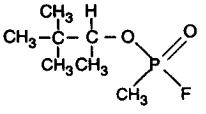
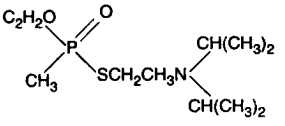
201. Introduction.

The nerve agents (NA) are a group of particularly toxic chemical warfare agents. They were developed just before and during World War II and are related chemically to the organophosphorus insecticides. The principle agents in this group are: GA (Tabun), GB (Sarin), GD (Soman), GF and VX (methylphosphonothioic acid). (In some countries the "V" agents are known as "A" agents.)

202. Physical and Chemical Properties.

a. Nerve agents are organophosphorus esters. The "G' agents tend to be non-persistent whereas the "V" agents are persistent. Some "G' agents may be thickened with various substances in order to increase their persistence, and therefore the total amount penetrating intact skin. The physical properties are given in Table 2-I.

Table 2-I. Physical Properties of Nerve Agents

Property	Tabun (GA)	Sarin (GB)	Soman (GD)	VX
Appearance	Colourless to brown liquid giving off colourless vapour	Colourless liquid giving off a colorless vapour	Colourless liquid giving off a colourless vapour	Amber coloured liquid
Chemical formula				
Molecular weight	162.12	140.10	182.2	267.4
Density ($g.cm^{-3}$ at 25°C)	1.07	1.09	1.02	1.01
Melting point	-50.0°C	-57.0°C	-42.0°C	-51.0°C
Boiling point	240.0°C	147.0°C	198.0°C	298.0°C
Vapour density	5.63	4.86	6.33	9.2
Vapour pressure (mmHg at 25°C)	0.07	2.9	0.4	0.007
Volatility ($mg.m^{-3}$)	90 (0°C) 610 (25°C) 858 (30°C)	4,100 (0°C) 22,000 (25°C) 29,800 (30°C)	531 (0°C) 3,900 (25°C) 5,570 (30°C)	10.5 (25°C)

b. It may be seen that at room temperature GB is a comparatively volatile liquid and therefore non-persistent. GD is also significantly volatile, as is GA though to a lesser extent. VX is a relatively non-volatile liquid and therefore persistent. It is regarded as presenting little vapour hazard to people exposed to it. In the pure state nerve agents are colorless and mobile liquids. In an impure state nerve agents may be encountered as yellowish to brown liquids. Some nerve agents have a faint fruity odour.

c. In general, nerve agents are moderately soluble in water with slow hydrolysis, highly soluble in lipids, rapidly inactivated by strong alkalis and chlorinating compounds.

203. Detection.

Nerve agents may be detected by a variety of means. Single and three colour detector papers are available for individual issue to detect liquid nerve agent. Area detectors are also available as are monitoring devices for local contamination and water testing kits.

204. Protection.

a. To prevent inhalation of an incapacitating or lethal dose it is essential that the breath is held and the respirator put on at the first warning of the presence, or suspected presence, of a nerve agent.

b. Normal clothing is penetrated by these agents whether contact is with liquid or vapour and specialised clothing including a respirator, nuclear, biological, and chemical (NBC) suit, gloves and overboots are required for protection when liquid agent is present. The respirator protects the eyes, mouth and respiratory tract against nerve agent spray vapour and aerosol. Nerve agent vapour in field concentrations is absorbed through the skin very slowly, if at all, so that where a vapour hazard exists alone, the respirator may provide adequate protection without the use of an NBC suit.

205. Decontamination.

a. The importance of early decontamination can not be over emphasised. Decontamination of the skin should be accomplished quickly if it is to be fully effective. Liquid agent may be removed by fullers' earth or chemically inactivated by the use of reactive decontaminants. Decontamination personnel should use a respirator and full protective equipment whilst decontamination is performed.

b. Once a casualty has been decontaminated, or the agent fully absorbed, no further risk of contamination exists. The casualty's body fluids, urine or faeces do not present a chemical warfare (CW) hazard.

206. Mechanism of Action.

a. *Absorption*. Nerve agents may be absorbed through any body surface. When dispersed as a spray or an aerosol, droplets can be absorbed through the skin, eyes and respiratory tract. When dispersed as a vapour at expected field concentrations, the vapour is primarily absorbed through the respiratory tract. If enough agent is absorbed, local effects are followed by generalised systemic effects. The rapidity

with which effects occur is directly related to the amount of agent absorbed in a given period of time.

b. *Inhibition by Agents.*

(1) The effects of the nerve agents are mainly due to their ability to inhibit acetylcholinesterase throughout the body. Since the normal function of this enzyme is to hydrolyse acetylcholine wherever it is released, such inhibition results in the accumulation of excessive concentrations of acetylcholine at its various sites of action. These sites include the endings of the parasympathetic nerves to the smooth muscle of the iris, ciliary body, bronchial tree, gastrointestinal tract, bladder and blood vessels; to the salivary glands and secretory glands of the gastrointestinal tract and respiratory tract; and to the cardiac muscle and endings of sympathetic nerves to the sweat glands. The accumulation of acetylcholine at these sites results in characteristic muscarinic signs and symptoms.

(2) The accumulation of acetylcholine at the endings of motor nerves to voluntary muscles and in some autonomic ganglia results in nicotinic signs and symptoms.

(3) The accumulation of excessive acetylcholine in the brain and spinal cord results in characteristic central nervous system symptoms. (See Table 2-II.)

(4) The inhibition of cholinesterase enzymes throughout the body by nerve agents may be irreversible and its effects prolonged.

(5) Treatment with oximes should begin promptly.

(6) Until the tissue cholinesterase enzymes are restored to normal activity, there is a period of increased susceptibility to the effects of another exposure to any nerve agent. The period of increased susceptibility occurs during the enzyme regeneration phase which could last from weeks to months, depending on the severity of the initial exposure. During this period the effects of repeated exposures are cumulative.

c. *Location of Acetylcholinesterase.* Acetylcholinesterase is found associated with the post-junctional membrane at the neuromuscular junction and in the cell bodies and processes of cholinergic neurons. The concentration is particularly high in some central nervous system neurons. The location of acetylcholinesterase in autonomic ganglia is less well understood than that at the neuromuscular junction. Acetylcholinesterase is also found at sites where, as yet, no functional role has been identified: the musculotendinous junction, red blood cells, platelets and the placenta.

d. *Further Information.* Further information on the action of nerve agents on acetylcholinesterase is given in Annex A.

207. Pathology.

Aside from the decrease in the activity of cholinesterase enzymes throughout the body (which may be detected by chemical methods or by special staining), no specific lesions are detectable by ordinary gross examination. At post-mortem examination there is usually capillary dilation, hyperaemia and oedema of the lungs; there may be similar changes in the brain and the remaining organs. Neuropathological changes have been reported in animals following severe intoxication. During the acute phase these include damage within the central nervous system and

at the neuromuscular endplate. Later on, following severe exposure to some nerve agent, lesions to the peripheral motor nerves may be identified.

Table 2-II. Likely Signs and Symptoms of GB Poisoning Shown in Terms of Vapour Exposure and Approximate Blood Acetylcholinesterase Depression

Short term Ct mg.min.m^{-3}	Approximate AChE depression	Symptoms and signs*	
		Vapour	Systemic exposure only eyes protected
<2	<5%	Incipient miosis (miosis produced at Ct=2, t=30 min), slight headache.	Nil.
5	20% ±10%	Increased miosis, headache, eye pain, rhinorrhoea, conjunctival injection, tightness in chest.	Tightness in chest.
5-15	20-50% ±10%	Eye signs maximal. Bronchospasm in some subjects.	Symptoms beginning to appear. Bronchospasm.
15	50%±10%	Bronchospasm and all the effects already described.	Wheezing, salivation, eye effects, nausea, vomiting. (Local sweating and fasciculation in liquid contamination of the skin.)
40	80%±10%	Symptoms and signs as for systemic exposure.	Weakness, defecation, urination, paralysis, convulsions.
100	100%	Respiratory Failure Death	Respiratory Failure Death

* All symptoms and signs will be subject to very considerable inter-subject variation.

SECTION II - EFFECTS OF NERVE AGENTS

208. Signs and Symptoms.

a. The order in which signs and symptoms appear and their relative severity depend on the route of exposure and whether the casualty has been exposed to liquid agent or vapour.
b. The signs and symptoms following exposure to nerve agents are given in Table 2-III.
c. The local effects of vapour and liquid exposure are described followed by a description of the systemic effects which occur after significant absorption of agent via any route.

209. Effects of Nerve Agent Vapour.

a. *Absorption.* The lungs and the eyes absorb nerve agents rapidly. Changes occur in the smooth muscle of the eye, resulting in miosis and in the smooth muscle and

secretory glands of the bronchi, producing bronchial constriction and excessive secretions in the upper and lower airways. In high vapour concentrations, the nerve agent is carried from the lungs throughout the circulatory system; widespread systemic effects may appear in less than 1 minute.

Table 2-III. Signs and Symptoms of Nerve Agent Poisoning

Site of action	Signs and symptoms
a. Muscarinic.	
(1) Pupils.	Miosis, marked, usually maximal (pin-point), sometimes unequal.
(2) Ciliary body.	Frontal headache, eye pain on focusing, blurring of vision.
(3) Nasal mucous membranes.	Rhinorrhoea, hyperaemia.
(4) Bronchial tree.	Tightness in chest, bronchoconstriction, increased secretion, cough.
(5) Gastrointestinal.	Occasional nausea and vomiting.
b. Muscarinic following systemic absorption (depending on dose).	
(1) Bronchial tree.	Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, dyspnoea, pain in chest, increased bronchial secretion, cough, cyanosis, pulmonary oedema.
(2) Gastrointestinal.	Anorexia, nausea, vomiting, abdominal cramps, epigastric and substernal tightness (cardiospasm) with "heartburn" and eructation, diarrhoea, tenesmus, involuntary defecation.
(3) Sweat glands.	Increased sweating.
(4) Salivary glands.	Increased salivation.
(5) Lachrymal glands.	Increased lachrymation.
(6) Heart.	Bradycardia.
(7) Pupils.	Miosis, occasionally unequal, later maximal miosis (pin-point).
(8) Ciliary body.	Blurring of vision, headache.
(9) Bladder.	Frequency, involuntary micturition.
c. Nicotinic.	
(1) Striated muscle.	Easy fatigue, mild weakness, muscular twitching, fasciculations, cramps, generalised weakness/flaccid paralysis (including muscles of respiration) with dyspnoea and cyanosis.
(2) Sympathetic ganglia.	Pallor, transitory elevation of blood pressure followed by hypotension.
d. Central nervous system.	Immediate (Acute) Effects: Generalised weakness, depression of respiratory and circulatory centres with dyspnoea, cyanosis and hypotension; convulsions, loss of consciousness and coma. Delayed (Chronic) Effects: Giddiness, tension, anxiety, jitteriness, restlessness, emotional lability, excessive dreaming, insomnia, nightmares, headaches, tremor, withdrawal and depression, bursts of slow waves of elevated voltage in EEG (especially on hyperventilation), drowsiness, difficulty concentrating, slowness of recall, confusion, slurred speech, ataxia.

b. *Local Ocular Effects.*

(1) These effects begin within seconds or minutes after exposure, before there is any evidence of systemic absorption. The earliest ocular effect which follows minimal symptomatic exposure to vapour is miosis. This is an invariable sign of ocular exposure to enough vapour to produce symptoms. It is also the last ocular manifestation to disappear. The pupillary constriction may be different in each eye. Within a few minutes after the onset of exposure, there also occurs redness of the eyes due to conjunctival hyperaemia, and a sensation of pressure with heaviness in and behind the eyes. Usually vision is not grossly impaired, although there may be a slight dimness especially in the peripheral fields or when in dim or artificial light.

(2) Exposure to a level of a nerve agent vapour slightly above the minimal symptomatic dose results in miosis, pain in and behind the eyes attributable to ciliary spasm, especially on focusing, some difficulty of accommodation and frontal headache. The pain becomes worse when the casualty tries to focus the eyes or looks at a bright light. Some twitching of the eyelids may occur. Occasionally there is nausea and vomiting which, in the absence of systemic absorption, may be due to a reflex initiated by the ocular effects. These local effects may result in moderate discomfort and some loss of efficiency but may not necessarily produce casualties.

(3) Following minimal symptomatic exposure, the miosis lasts from 24 to 72 hours. After exposure to at least the minimal symptomatic dose, miosis is well established within half an hour. Miosis remains marked during the first day after exposure and then diminishes gradually over 2 to 3 days after moderate exposure but may persist for as long as 14 days after severe exposure. The conjunctival erythema, eye pain, and headache may last from 2 to 15 days depending on the dose.

c. *Local Respiratory Effects.* Following minimal exposure, the earliest effects on the respiratory tract are a watery nasal discharge, nasal hyperaemia, sensation of tightness in the chest and occasionally prolonged wheezing expiration suggestive of bronchoconstriction or increased bronchial secretion. The rhinorrhoea usually lasts for several hours after minimal exposure and for about 1 day after more severe exposure. The respiratory symptoms are usually intermittent for several hours duration after mild exposure and may last for 1 or 2 days after more severe exposure.

210. Effects of Liquid Nerve Agent.

a. *Local Ocular Effects.* The local ocular effects are similar to the effects of nerve agent vapour. If the concentration of the liquid nerve agent contaminating the eye is high, the effects will be instantaneous and marked; and, if the exposure of the two eyes is unequal, the local manifestations may be unequal. Hyperaemia may occur but there is no immediate local inflammatory reaction such as may occur following ocular exposure to more irritating substances (for example, Lewisite).

b. *Local Skin Effects.* Following cutaneous exposure, there is localised sweating at and near the site of exposure and localised muscular twitching and fasciculation.

However, these may not be noticed causing the skin absorption to go undetected until systemic symptoms begin.

c. *Local Gastrointestinal Effects.* Following the ingestion of substances containing a nerve agent, which is essentially tasteless, the initial symptoms include abdominal cramps, vomiting and diarrhoea.

211. Systemic Effects of Nerve Agent Poisoning.

a. The sequence of symptoms varies with the route of exposure. While respiratory symptoms are generally the first to appear after inhalation of nerve agent vapour, gastrointestinal symptoms are usually the first after ingestion. Following comparable degrees of exposure, respiratory manifestations are most severe after inhalation, and gastrointestinal symptoms may be most severe after ingestion. Otherwise, the systemic manifestations are, in general, similar after any exposure to nerve agent poisoning by any route. If local ocular exposure has not occurred, the ocular manifestations (including miosis) initially may be absent.

b. The time course of effects following exposure to nerve agents are given in Table 2-IV.

c. The systemic effects may be considered to be nicotinic, muscarinic or by an action at receptors within the central nervous system. The predominance of muscarinic, nicotinic or central nervous system effects will influence the amount of atropine, oxime or anticonvulsant which must be given as therapy. These effects will be considered separately.

212. Muscarinic Effects of Nerve Agent Poisoning.

a. Tightness in the chest is an early local symptom of respiratory exposure. This symptom progressively increases as the nerve agent is absorbed into the systemic circulation, whatever the route of exposure. After moderate or severe exposure, excessive bronchial and upper airway secretions occur and may become very profuse, causing coughing, airway obstruction and respiratory distress. Audible wheezing may occur, with prolonged expiration and difficulty in moving air into and out of the lungs, due to the increased bronchial secretion or to bronchoconstriction, or both. Some pain may occur in the lower thorax and salivation increases.

b. Bronchial secretion and salivation may be so profuse that watery secretions run out of the sides of the mouth. The secretions may be thick and tenacious. If postural drainage or suction is not employed, these secretions may add to the airway obstruction. Laryngeal spasm and collapse of the hypopharyngeal musculature may also obstruct the airway. The casualty may gasp for breath, froth at the mouth, and become cyanotic.

c. If the upper airway becomes obstructed by secretions, laryngeal spasm or hypopharyngeal musculature collapse, or if the bronchial tree becomes obstructed by secretions or bronchoconstriction, little ventilation may occur despite respiratory movements. As hypoxaemia and cyanosis increase, the casualty will fall exhausted and become unconscious.

Table 2-IV. Time Course of Effects of Nerve Agents

Nerve agent	Types of effects	Route of absorption	Description of effects	When effects appear after exposure*	Duration of effects after:	
					Mild exposure	Severe exposure
Vapour.	Local.	Lungs.	Rhinorrhoea, nasal hyperaemia, tightness in chest, wheezing.	One to several minutes.	A few hours.	1 to 2 days.
Vapour.	Local.	Eyes.	Miosis, conjunctival hyperaemia, eye pain, frontal headache.	One to several minutes.	Miosis 24 hours.	2 to 3 days.
Vapour.	Systemic.	Lungs or eyes.	Muscarinic, nicotinic, and central nervous system effects.(See Table 3-I).	Less than one minute to a few minutes after moderate or severe exposure.	Several hours to a day.	Acute effects: 2 to 3 days. CNS effects: days to weeks.
Liquid.	Local.	Eyes.	Same as vapour effects.	Instantly.	Similar to effects of vapour.	
Liquid.	Local.	Ingestion.	Gastrointestinal. (See Table 3-I).	About 30 minutes after ingestion.	Several hours to a day.	2 to 5 days.
Liquid.	Local.	Skin.	Local sweating and muscular twitching.	3 minutes to 2 hours.	3 days.	5 days.
Liquid.	Systemic.	Lungs.	See Table (3-I).	Several minutes.		1 to 5 days.
Liquid.	Systemic.	Eyes.	Same as for vapour.	Several minutes.		2 to 4 days.
Liquid.	Systemic.	Skin.	Generalised sweating.	15 minutes to 2 hours.		2 to 5 days.
Liquid.	Systemic.	Ingestion.	Gastrointestinal. (See Table 3-I).	15 minutes to 2 hours.		3 to 5 days.

* After lethal or near lethal exposures to nerve agents, the time to onset of symptoms and to maximal severity of symptoms is shorter; it may be extremely brief after overwhelming exposure. Following exposure to lethal concentrations, the time interval to death depends upon the degree, the route of exposure, and the agent. If untreated, exposure to lethal concentrations of nerve agents can result in death 5 minutes after appearance of symptoms.

d. Following inhalation of nerve agent vapour, the respiratory manifestations predominate over the other muscarinic effects: they are likely to be most severe in older casualties and in those with a history of respiratory disease, particularly bronchial asthma. However, if the exposure is not so overwhelming as to cause death within a few minutes, other muscarinic effects appear. These include sweating, anorexia, nausea and epigastric and substernal tightness with heartburn and eructation. If absorption of nerve agent has been great enough (whether due to a single large exposure or to repeated smaller exposures), there may follow abdominal cramps, increased peristalsis, vomiting, diarrhoea, tenesmus, increased lachrymation and urinary frequency. Cardiovascular effects are a bradycardia, hypotension and cardiac arrhythmias. The casualty perspires profusely, may have involuntary defecation and urination and may go into cardiorespiratory arrest followed by death.

213. Nicotinic Effects.

a. With the appearance of moderate muscarinic systemic effects, the casualty begins to have increased fatiguability and mild generalised weakness which is increased by exertion.

b. This is followed by involuntary muscular twitching, scattered muscular fasciculations and occasional muscle cramps. The skin may be pale due to vasoconstriction and blood pressure moderately elevated (transitory) together with a tachycardia, resulting from cholinergic stimulation of sympathetic ganglia and possibly from the release of epinephrine. If the exposure has been severe, the muscarinic cardiovascular symptoms will dominate and the fascicular twitching (which usually appear first in the eyelids and in the facial and calf muscles) becomes generalised. Many rippling movements are seen under the skin and twitching movements appear in all parts of the body. This is followed by severe generalised muscular weakness, including the muscles of respiration. The respiratory movements become more laboured, shallow and rapid; then they become slow and finally intermittent. Later, respiratory muscle weakness may become profound and contribute to the respiratory depression. Central respiratory depression may be a major cause of respiratory failure.

214. Central Nervous System Effects.

a. In mild exposures, the systemic manifestations of nerve agent poisoning usually include tension, anxiety, jitteriness, restlessness, emotional lability, and giddiness. There may be insomnia or excessive dreaming, occasionally with nightmares.

b. If the exposure is more marked, the following symptoms may be evident: headache, tremor, drowsiness, difficulty in concentration, impairment of memory with slow recall of recent events, and slowing of reactions. In some casualties there is apathy, withdrawal and depression. With the appearance of moderate symptoms, abnormalities of the electroencephalogram occur, characterised by irregularities in rhythm, variations in potential, and intermittent bursts of abnormally slow waves of elevated voltage similar to those seen in patients with epilepsy. These abnormal waves become more marked after one or more minutes of hyperventilation which, if prolonged, may occasionally precipitate a generalised convulsion.

c. If absorption of nerve agent has been great enough, the casualty becomes confused and ataxic. The casualty may have changes in speech, consisting of slurring, difficulty in forming words, and multiple repetition of the last syllable. The casualty may then become comatose, reflexes may disappear and respiration may become Cheyne-Stokes in character. Finally, generalised convulsions may ensue.

d. With the appearance of severe central nervous system symptoms, central respiratory depression will occur (adding to the respiratory embarrassment that may already be present) and may progress to respiratory arrest. However, after severe exposure the casualty may lose consciousness and convulse within a minute without other obvious symptoms. Death is usually due to respiratory arrest and anoxia, and requires prompt initiation of assisted ventilation to prevent death. Depression of the

circulatory centres may also occur, resulting in a marked reduction in heart rate with a fall of blood pressure some time before death.

215. Cumulative Effects of Repeated Exposure.

a. Daily exposure to concentrations of a nerve agent insufficient to produce symptoms following a single exposure may result in the onset of symptoms after several days. Continued daily exposure may be followed by increasingly severe effects.

b. After symptoms subside, increased susceptibility may persist for up to 3 months. The degree of exposure required to produce recurrence of symptoms and the severity of these symptoms depend on the dose received and the time interval since the last exposure. Increased susceptibility is not limited to the particular nerve agent initially absorbed.

216. Cause of Death.

a. In the absence of treatment, death is caused by anoxia resulting from airway obstruction, weakness of the muscles of respiration and central depression of respiration.

b. Airway obstruction is due to pharyngeal muscular collapse, upper airway and bronchial secretions, bronchial constriction and occasionally laryngospasm and paralysis of the respiratory muscles.

c. Respiration is shallow, laboured, and rapid and the casualty may gasp and struggle for air. Cyanosis increases. Finally, respiration becomes slow and then ceases. Unconsciousness ensues. The blood pressure (which may have been transitorily elevated) falls. Cardiac rhythm may become irregular and death may ensue.

d. If assisted ventilation is initiated via cricothyroidotomy or endotracheal tube and airway secretions are removed by postural drainage and suction and diminished by the administration of atropine, the individual may survive several lethal doses of a nerve agent. However, if the exposure has been overwhelming, amounting to many times the lethal dose, death may occur despite treatment as a result of respiratory arrest and cardiac arrhythmia.

e. When overwhelming doses of the agent are absorbed quickly, death occurs rapidly without orderly progression of symptoms.

SECTION III - TREATMENT OF NERVE AGENT POISONING

217. Diagnosis and Therapy of Nerve Agent Poisoning.

a. *Symptoms.* Nerve agent poisoning may be identified from the characteristic signs and symptoms. If exposure to vapour has occurred, the pupils will be very small, usually pin-pointed. If exposure has been cutaneous or has followed ingestion of a nerve agent in contaminated food or water, the pupils may be normal or, in the presence of severe systemic symptoms, slightly to moderately reduced in size. In this event, the other manifestations of nerve agent poisoning must be relied on to establish the diagnosis. No other known chemical agent produces muscular twitching and

fasciculations, rapidly developing pin-point pupils, or the characteristic train of muscarinic, nicotinic and central nervous system manifestations.

b. *Symptom Differentiation.* It is important that individual service members know the following MILD and SEVERE signs and symptoms of nerve agent poisoning. Service members who have most or all of the symptoms listed below must IMMEDIATELY receive first aid (self-aid or buddy aid respectively).

c. *MILD Poisoning (Self-Aid).* Casualties with MILD symptoms may experience most or all of the following:

(1) Unexplained runny nose.
(2) Unexplained sudden headache.
(3) Sudden drooling.
(4) Difficulty in seeing (dimness of vision and miosis).
(5) Tightness in the chest or difficulty in breathing.
(6) Localised sweating and muscular twitching in the area of the contaminated skin.
(7) Stomach cramps.
(8) Nausea.
(9) Bradycardia or tachycardia.

d. *MODERATE Poisoning.* Casualties with MODERATE poisoning will experience an increase in the severity of most or all of the MILD symptoms. Especially prominent will be an increase in fatigue, weakness and muscle fasciculations. The progress of symptoms from mild to moderate indicates either inadequate treatment or continuing exposure to agent.

e. *SEVERE Symptoms (Buddy Aid).* Casualties with SEVERE symptoms may experience most or all of the MILD symptoms, plus most or all of the following:

(1) Strange or confused behaviour.
(2) Wheezing, dyspnoea (severe difficulty in breathing), and coughing.
(3) Severely pin-pointed pupils.
(4) Red eyes with tearing.
(5) Vomiting.
(6) Severe muscular twitching and general weakness.
(7) Involuntary urination and defecation.
(8) Convulsions.
(9) Unconsciousness.
(10) Respiratory failure.
(11) Bradycardia.

f. *Aid for Severe Cases.* Casualties with severe symptoms will not be able to treat themselves and must receive prompt buddy aid and follow-on medical treatment if they are to survive.

218. Treatment.

The lethal effects of nerve agent poisoning may be combated by a combination of pretreatment and post exposure therapy.

219. Pretreatment.

a. Poisoning by nerve agents which form rapidly aging complexes (for example Soman) may be particularly difficult to treat. These difficulties have been solved, in part, by the use of carbamates as pretreatment. The terms pretreatment or prophylaxis should perhaps be defined as used in this context:
   (1) Pretreatment: the administration of drugs in advance of poisoning designed to increase the efficacy of treatment administered post-poisoning.
   (2) Prophylaxis: the administration of drugs in advance of the poisoning designed to make post-poisoning therapy unnecessary.

b. The terms are to an extent interchangeable and as, in cases of severe poisoning, post-poisoning therapy is nearly always needed, the term pretreatment will be used here.

c. Carbamate anticholinesterases, e.g., pyridostigmine, may be used as pretreatment against nerve agent poisoning by virtue of their capacity to bind acetylcholinesterase *reversibly,* preventing the organophosphate (OP) binding to the enzyme. The term reversible is here used comparatively: the carbamate-acetylcholinesterase complex breaks down fairly rapidly, while organophosphate-acetylcholinesterase complexes break down very slowly. The aged soman-acetylcholinesterase complex breaks down virtually not at all.

d. When carbamates are used as pretreatments, carbamoylation of acetylcholinesterase prevents phosphorylation, but later the carbamate-acetylcholinesterase complex dissociates, freeing active enzyme. Current pretreatment regimes bind 30-40% of available red blood cell acetylcholinesterase, thereby allowing the carbamate to protect some of the acetylcholinesterase against attack by nerve agent.

e. The carbamate pyridostigmine, given in a dose of 30 mg every 8 hours, is used as a pretreatment. In conjunction with post exposure therapy, good protection against lethality is obtained within 2 hours of the first dose, but is not optimal until the third dose.

f. Pyridostigmine pretreatment should be stopped upon developing symptoms of nerve agent poisoning following a chemical warfare attack and post exposure therapy started.

g. Pyridostigmine tablets were taken over a 4 to 5 day period by large numbers of troops during the Gulf War of 1991.
   (1) The effects of pyridostigmine were examined in several studies including one uncontrolled study of 42,000 troops when, following the recommended dose regime, under the stress of combat conditions, gastrointestinal intestinal changes including increased flatus, loose stools, abdominal cramps and nausea were noted by approximately half the population. Other reported effects were urinary urgency, headache, rhinorrhoea, diaphoresis and tingling of the extremities. These effects were considered tolerable. They did not noticeably interfere with performance of the full range of demanding physical and mental tasks required of service personnel.
   (2) Symptoms due to pyridostigmine may be ameliorated by taking the tablets with food.
   (3) Pyridostigmine pretreatment was discontinued on medical advice in less than 0.1 % of individuals, generally because of intolerable nausea and diarrhoea.

h. When taken in excess of the recommended dosage, symptoms of carbamate poisoning will occur. These include diarrhoea, gastrointestinal cramps, tight chest, nausea, rhinorrhoea, headache and miosis.

i. Good compliance is required if optimal protection is to be obtained. The importance of pyridostigmine pretreatment should therefore be stressed during training.

220. Post-Exposure Therapy.

The main principles of therapy for nerve agent poisoning are early treatment, assisted ventilation, bronchial suction, muscarinic cholinergic blockade (atropine), enzyme reactivation (oximes) and anticonvulsants (benzodiazepines).

221. Emergency Field Therapy.

a. *Self Aid (or Buddy Aid).*

(1) This comprises first aid measures which the soldier can apply to help him or herself. The rapid action of nerve agents call for immediate self treatment. Unexplained nasal secretion, salivation, tightness of the chest, shortness of breath, constriction of pupils, muscular twitching, or nausea and abdominal cramps call for the immediate intramuscular injection of 2 mg of atropine, combined if possible with oxime. From 1 to 3 automatic injection devices, each containing 2 mg atropine or mixture of atropine, oxime and/or anticonvulsant, are carried by each individual.

(2) One device should be administered immediately when the symptoms and/or signs of nerve agent poisoning appear. This may be done by the casualty or by a buddy; the injection being given perpendicularly through the clothing into the lateral aspect of the middle of the thigh. Further devices, up to a total of 3, should be administered by the casualty or by his or her buddy during the following 30 minutes if the symptoms and/or signs of poisoning fail to resolve.

(3) The timing of these further injections and whether they are given at one time or separately may depend on the casualty's condition and on instructions promulgated by individual nations.

(4) NOTE: If automatic injectors are used in the absence of exposure to agent, the following signs and symptoms may be seen: Dry mouth, dry skin, fast pulse (>90 beats per minute), dilated pupils, retention of urine and central nervous system disturbance. Susceptibility to heat exhaustion or heat stroke is increased, particularly in closed spaces or while wearing protective clothing.

b. *First Aid by Trained Personnel.*

(1) This comprises the emergency actions undertaken to restore or maintain vital bodily functions in a casualty. Wherever the casualty is not masked the respirator must be adjusted for him or her by the nearest available person. Attention should be given to decontamination at the earliest possible moment

and any skin contamination must be removed with a personal decontamination kit.

(2) After nerve agent poisoning, the administration of atropine is repeated at intervals until signs of atropinization (dry mouth and skin and tachycardia >90 per minute) are achieved. Miosis from vapour exposure is not relieved by systemic atropine.

(3) Mild atropinization should be maintained for at least 24 hours by intramuscular injection of 1-2 mg of atropine at intervals of ½ to 4 hours, as required. The danger of ventricular arrhythmias arising from atropinization while the casualty is anoxic must be remembered.

(4) Assisted ventilation is required for severely poisoned individuals as they will have:

(a) Marked bronchoconstriction;

(b) Copious secretions in the trachea and bronchi;

(c) Paralysis of the respiratory muscles; and

(d) Central respiratory depression, hypoxia, and convulsions.

c. *Resuscitation.*

(1) Positive pressure resuscitation should be given but the pressure necessary to overcome the bronchoconstriction may be more than 65 cm of water so that incubation if possible is highly desirable. In an uncontaminated atmosphere assisted ventilation may be done by the standard mouth-to-mouth method after decontamination of the casualty's face and mouth. In a contaminated atmosphere ventilation may be given by a portable resuscitator with NBC filter attached. Both the casualty and the resuscitator should be decontaminated.

(2) In a well equipped medical facility, mechanical resuscitation of the positive pressure type may be used with endotracheal incubation or tracheostomy-artificial respiration must be continued until the casualty is breathing normally or the medical personnel have pronounced the casualty dead. Due to the production of copious secretions, regular suction will be required.

222. Pharmacological Treatment of Nerve Agent Poisoning.

a. The pharmacological treatment of nerve agent poisoning involves the use of

(1) Anticholinergics to antagonise the muscarinic effects (atropine).

(2) Oximes to reactivate inhibited enzyme.

(3) Anticonvulsants to prevent CNS damage.

b. The effects of drugs used in nerve agent poisoning are described below.

223. Atropine.

a. Atropine sulphate remains an essential drug in the treatment of nerve agent poisoning. It acts by blocking the effects of acetylcholine at muscarinic receptors and so produces relief from many of the symptoms previously listed. If given in large doses, some therapeutic effects are also produced within the central nervous system

although atropine does not readily penetrate the blood brain barrier and central muscarinic receptors are thought not to be identical with those in the periphery. It is thought to counteract the respiratory depression in the medulla oblongata.

b. Urgent treatment with atropine in cases of nerve agent poisoning is essential. After the emergency field treatment, atropinisation should be maintained for at least 24 hours by intramuscular injection or slow intravenous infusion of 1 to 2 mg of atropine per hour as required. The dose should be repeated at intervals until signs of successful atropinisation are noted. Intervals of 5 to 15 minutes seem reasonable, but severe poisoning may require higher doses (4 mg to 6 mg per hour or more). Signs of successful atropinisation include the drying up of bronchial, salivary and skin secretions and an increase in heart rate to greater than 90 beats per minute.

c. The effect of atropine in drying bronchial secretions may make the removal of mucus more difficult so suction is likely to be necessary. In excessive doses, atropine may render the ischaemic myocardium more liable to arrhythmias and electrocardiogram (ECG) monitoring should be undertaken in all patients if possible.

d. Atropine overdosage may produce euphoria, hallucinations, anxiety, and delirium and close observation of patients is necessary. Bladder dysfunction may necessitate catheterisation.

e. By inhibition of sweat production, atropine increases heat stress and in warm or hot weather care must be taken to avoid hyperthermia.

f. Atropine given parenterally has comparatively little effect on nerve agent induced miosis. The local application of cycloplegics (atropine eye drops) to the eye reduces both the degree of rniosis, eye pain and headache. However, expert opinion on the value of atropine containing eye drops in the management of nerve agent induced miosis remains divided. It is believed by some that problems of accommodation may be made worse by the application of the drops and that, overall, little benefit may be produced.

g. If atropine is administered in the absence of nerve agent poisoning, the following effects may be noted: dryness of the mouth and pharynx, decreased sweating, slight flushing and tachycardia, some hesitancy of micturition, slightly dilated pupils, mild drowsiness, slowness of memory and recall and blurring of near vision. After 2mg these symptoms should not interfere with ordinary activity except in the occasional person, in hot environments or at high work rates. Higher doses, or repeated doses, will produce more marked symptoms which will usually not be totally incapacitating except in warm environments or high work rates. The effects of atropine are fairly prolonged, lasting 3 to 5 hours after one or two injections of 2mg and 12 to 24 hours after marked over-atropinisation.

224. Oximes.

a. *Oximes.*

(1) While atropine blocks the muscarinic effects of nerve agent poisoning it has little effect upon the nicotinic actions of the agent at the skeletal neuromuscular junction and at the autonomic ganglia.

(2) Amelioration of the effects of nerve agents at these sites and also at

muscarinic sites can, however, be obtained by reactivation of the inhibited acetylcholinesterase by means of oximes. Oximes, therefore, relieve the clinically important symptom of skeletal neuromuscular blockade. However, they penetrate into the central nervous system poorly, and the simultaneous administration of atropine is therefore still required.

b. *Enzyme Reactivation.*

(1) The relative potency of different oximes in reactivating acetylcholinesterase inhibited by some nerve agents is given in Table 2-V.

(2) Dosing schemes for the clinical intravenous use of currently available oximes, as applied in poisoning of humans by organophosphate insecticides, are shown in Table 2-VI. Under field conditions similar doses can be given intramuscularly, but care should be taken to avoid accidental intra-arterial injection. The dose rates given could form the base for the determination of national dosing procedures which should include emergency field treatment.

Table 2-V. Effectiveness of Various Oximes in the Treatment of Nerve Agent Poisoning

Oxime	GA	GB	GD	GF
P_2S	-	+	-	-
Obidoxime	+	+	-	+/-
HI6	+/-	+	+/-	+

+ = Effective
+/- = Sometimes effective
- = Not effective

Table 2-VI. Examples of Current Dosing Scheme for the Intravenous Administration of Oximes

Degree of poisoning	PAM Cl dose	P_2S dose	Obidoxome dose
Mild	1 g	400 mg	250 mg
Moderate	1 g*	400 mg**	250 mg***
Severe	1 g*	500 mg**	250 mg***

* To be repeated every 8 to 12 hours.
** Second dose of 400 mg to 500 mg after 30 minutes. Further doses of 200 mg to 400 mg every 4 to12 hours.
*** Second dose after 2 hours. Further doses to be repeated every 6 to 12 hours.

(3) An alternative method of administering oxime is as a continuous infusion. On the basis of a theoretical therapeutic plasma concentration of 4mg.1-[1], the loading dose and maintenance dose for intravenous use can be calculated for different oximes using data obtained in healthy human volunteers (Table 2-VII). Data from human organophosphorus insecticide poisoning suggest that these dose rates are also applicable in patients.

(4) Clinical experience in human poisoning by organophosphorus insecticide shows that oxime treatment should be continued for some hours after reactivation has been obtained and the patient has recovered. If no enzyme reactivation has been obtained after a 24 to 48 hour period of treatment and the patient has not recovered, then it should be accepted that the enzyme inhibition is resistant to reactivation by the particular oxime and administration should be stopped. There is only limited experience with human poisoning with organophosphorus nerve agents, but animal data suggest that the clinically relevant persistence of nerve agent in the body will probably be shorter than for insecticides. It may be suggested therefore, that oxime treatment should be continued until the recovery of the patient, with a probable maximum duration of 24 to 48 hours.

c. *Oxime Induced Side Effects.* The rapid injection of pralidoxime 2 (PAM Cl or P_2S) can produce drowsiness, headache, disturbance of vision, nausea, dizziness, tachycardia and an increase in blood pressure, hyperventilation and muscular weakness. Obidoxime produces hypotension, a menthol-like sensation and a warm feeling in the face. On intramuscular injection, it can produce a dull pain at the site of injection; after multiple dosing, hepatic dysfunction can be observed. HI6 (a type of oximide) produces similar effects.

Table 2-VII. Loading Doses and Infusion Rates for Oxime Administration to Obtain a Plasma Concentration of 4 mg.1^{-1}

Oxime	Loading dose** ($mg.kg^{-1}$)	Approximate dose for 70 kg person (mg)	Infusion rate*** ($mg.kg^{-1}.h^{-1}$)	Approximate rate for 70 kg person ($mg.h^{-1}$)
PAM Cl	4.2	300	2.2	160
P_2S	4.4	310	2.1	150
Obidoxime	0.8	56	0.5	34
HI6*	1.6	110	0.8	54

* Based on data from intramuscular administration.
** Loading dose = therapeutic plasma concentration x volume of distribution.
*** Infusion rate = therapeutic plasma concentration x clearance.

225. Anticonvulsants.

a. Atropine protects only partially against convulsions and the resulting brain damage in severe poisoning. Complementary treatment, including anticonvulsants, should be applied as necessary.

b. It has been shown in experimental soman poisoning that diazepam antagonises the convulsive action of soman and that addition of diazepam to the basic treatment regime greatly improves morbidity and mortality, independent of its anticonvulsive effect. Diazepam is the drug of choice and should be injected intramuscularly as a 10 mg dose initially and further doses should be given frequently enough to control convulsions. This may require injections at intervals ranging from a few minutes to several hours.

226. Supportive Care.

Although pre and post exposure therapy will protect against lethality, casualties may still be incapacitated. A patient severely poisoned by an anticholinesterase is a critical medical emergency and may require intensive care for days or weeks. Assisted ventilation may be needed for many hours or days and the patient may be comatose for hours or days and brain damage may result from periods of hypoxia. General supportive care such as IV feeding, restoring electrolyte balance, treatment of shock and control of convulsions is needed. Therapy to control infection, should this occur, should be on the usual lines. Special care should betaken using muscle relaxants in patients poisoned by nerve agents.