Chapter 11

INCAPACITATING AGENTS

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INTRODUCTION

As defined in *The American Heritage Dictionary of the English Language*, to "incapacitate" means "to deprive of strength or ability." The word is not synonymous with paralysis, confusion, or any other specific affliction. It is a general term, implying neither global inability to act nor any particular type of disability. For example, blurred near vision might be incapacitating for a computer programmer or air traffic controller but probably would not be incapacitating for a laborer or a football player. Consequently, when the word incapacitating is used, we should ask, "incapacitating for what activity?"

Used in a military context, incapacitation is understood to mean inability to perform one's military mission. Since missions vary, we could theoretically consider a particular agent to be incapacitating if it disrupts aspects of performance vital to a particular mission. Impaired hearing might incapacitate a translator, a severe tremor might incapacitate a sniper, and so forth. In this chapter, however, incapacitation means the inability to perform *any* military task effectively and implies that the condition was achieved via the deliberate use of a *nonlethal* weapon.

Finding a suitable nonlethal weapon to substitute for a lethal one poses formidable problems. Consider the criteria—military, medical, and budgetary—that should govern the selection of an ideal

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EXHIBIT 11-1

CRITERIA FOR THE IDEAL INCAPACITATING AGENT

1.	Effectiveness	The agent must be able to severely impair or completely disrupt an enemy's ability to fight.
2.	Relative lack of toxicity	When used as intended, the agent must produce few deaths or permanent injuries.
3.	Persistence	Effects must be temporary: preferably minutes to hours; at most, a few days.
4.	Logistical feasibility	The compound must be potent, chemically stable, and capable of being incorporated into practical munitions.
5.	Treatability	Effects brought about by the agent should be fully or partially reversible by relatively simple medical treatment. Even without treatment, ill effects should not cause permanent disability.
6.	Predictability	The behaviors produced by the agent must be relatively predictable and unlikely to bring about disastrous secondary consequences to civilians or other noncombatants. Nor should the agent increase the likelihood of the senseless activation of weapons of mass destruction by affected individuals.
7.	Manageability of casualties	Once captured, incapacitated individuals should be controllable. Deaths and injuries due to an interaction between the altered mental state and natural dangers in the immediate environment must be prevented.
8.	Expense	The cost of production must be affordable within the context of the overall military budget.

Source: Departments of the Army, Navy, and Air Force, and Commandant, Marine Corps. *Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries.* Washington, DC: HQ: DA, DN, DAF, Commandant, MC; 22 Dec 95: 3–1. Field Manual 8-285, NAVMED P-5041, Air Force Joint Manual 44-149, Fleet Marine Force Manual 11-11.

incapacitating agent: effectiveness, relative lack of toxicity, persistence, logistical feasibility, treatability, predictability, manageability of casualties, and expense (Exhibit 11-1). No proposed incapacitating agent meets all of these demanding requirements, but any compound worthy of standardization (ie, production without further modification) needs to fulfill most of them.

Further considerations would come into play before such an agent could be used. For example, methods and equipment must be designed to manufacture, store, and transport the agent. Troops in the field would need training to operate what might prove to be quite complex delivery systems. Medical personnel would need to learn how best to treat casualties, working within the confines of the battlefield.

USE OF INCAPACITATING AGENTS

Historical Precedents

Few references to the historical use of drugs for military purposes appear in contemporary publications. Scholars interested in chemical warfare, therefore, may easily assume that this concept is of recent origin, arising out of the technological revolution of the late 20th century. Actually, a substantial literature describing a variety of tactical efforts to incapacitate enemy forces by intoxicating them with mind-altering chemicals is available. The fact that such material is rarely cited in current publications, both lay and professional, probably has several explanations. The exponential expansion of pharmaceutical discovery, for example, has shifted attention from those few drugs that were the mainstay of medical treatment before the turn of the century. In addition, in the wake of an explosion of new information and the exponential proliferation of journals and textbooks, the older literature has been eclipsed and is rarely included in current indexes and computerized databases.

In 1961, Goodman[1] carried out a systematic perusal of 100 years of four leading American and British medical journals (*Journal of the American Medical Association, Boston Medical and Surgical Journal* [continued as *New England Journal of Medicine*], *Lancet*, and *British Medical Journal*) and a more limited survey of several respected German medical periodicals (*Fuhner-Wielands Sammulung von Vergiftungsfallen* [continued as *Archiv fur Toxikologie*] 1930–1961, and *Deutsche Zeitschrift fur die Gersamte Gerichtliche Medizin* 1922–1939). Goodman uncovered an astonishing variety of reports of the deliberate pharmacological induction, particularly by atropine and related drugs, of "behavioral toxicity" (a term introduced by Brady in 1956). Most of these were individual cases of poisoning for nefarious purposes, but many can be considered instances of the early use of drugs as "weapons of mass destruction" (a late–20th-century term that seemingly does not ethically distinguish nonlethal incapacitating chemical agents from lethal chemical agents, or from biological and nuclear weapons).

A few excerpts from Goodman's lengthy historical review are worthy of inclusion here, if only to show that incapacitating agents are by no means a new approach to military conflict:

> According to Sextus Julius Frontinus, Maharbal, an officer in Hannibal's army about 200 BC,…sent by the Carthaginians against the rebellious Africans, knowing that the tribe was passionately fond of wine, mixed a large quantity of wine with mandragora, which in potency is something between a poison and a soporific. Then, after an insignificant skirmish, he deliberately withdrew. At dead of night, leaving in the camp some of his baggage and all the drugged wine, he feigned flight. When the barbarians captured the camp and in frenzy of delight greedily drank the drugged wine, Maharbal returned, and either took them prisoners or slaughtered them while they lay stretched out as if dead.[2(p139)]
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> Another example of the use of atropinic plants for military purposes occurred during the reign of Duncan, the 84th King of Scotland (AD 1034–1040), who used wine dosed with "sleepy nightshade" against the troops of Sweno, King of Norway. After a battle near Culross, Duncan sent messengers to Sweno to negotiate surrender, and during the discussions supplied the Norwegians with provisions. As expected, this was looked on as a sign of weakness. The Scottish forces under Bancho entered Sweno's camp while the invaders were intoxicated and rapidly vanquished them.[3,4(pp537–538),5]
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> During his assault in 1672 on the city of Groningen, the Bishop of Muenster tried to use grenades and projectiles containing belladonna against the defender. Unfortunately, capricious winds often blew the smoke back, creating effects opposite to those intended. As a result of this and other incidents in which chemicals were used in battle, a treaty was signed in 1675 between the French and the Germans, outlawing further use of chemical warfare.[4(p563)]

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In 1813 the inhabitants of an area being invaded by French troops received fortuitous help from local flora. A company of starving French soldiers was rendered helpless when they impulsively consumed wild berries containing belladonna alkaloids. Gaultier, the company surgeon, vividly recorded the generalized confusion and self-destruction that took place as delirious soldiers wandered half-clothed through the bog. Others, in response to their hallucinations, cried out "Aux armes!" and threw themselves into blazing campfires.[6]

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Later in the same century a peaceful railway surveying expedition under Lieutenant-Colonel Paul Flatters was proceeding to the Sudan from Algeria, through the territory of the Touareg. These Barbers, who, unlike other North African, veil the men and not the women, are a raider people who did not completely surrender to French authorities until 1943. They called themselves "the Blue Men" and "the People of the Veil"; the other inhabitants, however, called them "the Abandoned of God."[7,8]

Flatters, ignoring a warning letter from the Touareg marched into an ambush on 16 February 1881, losing approximately the entire "assault group," which constituted half of his entire force. As his sixty-one remaining personnel tried to march to a French Outpost, they were trailed by approximately two hundred Touareg. On 8 March 1881, their supplies having been observed to be low, they were approached by three men who claimed to be members of another tribe. They were sold three bundles of dried dates, which were thrown into their camp the following day, and consumed in varying quantities by the troops. Shortly thereafter they exhibited the signs of solanaceous intoxication.[9]

Five men disappeared in the first minutes of confusion, and 31 of the remainder were so sick that they were unable to look after themselves. In the evening some attempted to crawl away into the desert. The other Frenchmen had been tied down by the senior indigenous soldier to prevent injury. The next morning, somewhat improved, "…they set off, half mad, bent double under excruciating pain, their legs crumbling away under them, their voices shrill, their words unintelligible." On the second day after the poisoning they reached an oasis, where a force of Touareg awaited them. By this time, however, the survivors were able to function as an effective fighting force and repulsed the attack. After finding water, and resorting to cannibalism to sustain life, 12 of the original soldiers reported to a French outpost 20 days after their initial "chemical warfare attack" by an "incapacitating agent" (later identified as *Hyoscyamus falezlez*).[9]

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Ironically, the first recorded 20th century use of solanaceae in a military situation occurred in Hanoi, French Indo-China (later known as North Vietnam) on 27 June 1908. On that day, two hundred French soldiers were poisoned by datura in their evening meal. One of the intoxicated soldiers saw ants on his bed, a second fled to a tree to escape from an hallucinated tiger and a third took aim at birds in the sky. The delirious troops were soon discovered and all recovered after medical attention. Two indigenous non-commissioned officers and an artilleryman were later convicted by courts-martial of plotting with ex-river pirates who had been influenced by "Chinese reformer agitators."[10,11]

Goodman's scholarly review[1] provides other examples, including the alleged use of cauldrons of burning hemp (containing tetrahydrocannabinol) or smoke from opium (morphine alkaloids) dating as far back as the first century BC; however, the foregoing examples should suffice to correct the notion that incapacitating chemical weapons are a modern invention.

Contemporary Use

Although warfare is tantamount to death and destruction, the international community, particularly in the latter half of the 20th century, has repeatedly tried to find ways to make war more "humane." Remorse and indignation were widely expressed following the use during World War I of such repugnant weapons as chlorine, mustard, and phosgene, which killed or injured hundreds of thousands of soldiers in the European trenches. One consequence of this outcry was an international ban on chemical weapons adopted by the Geneva Convention in 1925. The United States, although not a signatory to this document until 1975, strongly supported its purpose.

Chemical weapons were apparently not used during World War II, although the German military was later found to have developed and stockpiled several different lethal anticholinesterase nerve agents. Fortunately they were not used, perhaps because of the swift and overwhelming invasion by Allied forces. Following the end of the war in 1945, research and development of nerve agents (GA [tabun], GB [sarin], and later GD [soman] and VX) continued in a number of countries, including the United States. Other than in a few isolated instances, however, (such as the Iraqi use against Iran in the 1980s) these agents have not been used in warfare. They remain in the United States

arsenal, presumably as defensive weapons of last resort.

What was thought to be a novel concept—using chemicals to produce temporary disability—began to attract increasing interest as the acceptance of lethal agents declined. (As Goodman reported, of course, attempts to use various drugs and potions for this purpose are nothing new.) As credible military weapons, however, drugs did not receive serious consideration until the 1950s, when scientific psychopharmacology first came of age. At about this time, a number of research laboratories began to explore this possibility. During the next two decades, the feasibility of chemical incapacitation was systematically studied by nations on both sides of the Iron Curtain. The following, also from Goodman's review, might be considered an example of "Cold War chemical warfare"[1]:

A double agent revealed that in Munich, in 1959, salt shakers in a cafeteria serving 1,248 employees of Radio Free Europe were dosed with atropine. Chemical analysis of the contents of two shakers showed the presence of 2.36 per cent by weight of atropine.[12,13] (One gram of this concoction would thus contain almost 24 mg of atropine, more than enough to produce severe delirium.) Fortunately, the attempt was aborted.

In the United States, substantial resources were allocated for this study, reaching a peak in the mid-1960s. After extensive clinical study, a single incapacitating agent (BZ) was chosen for standardization by the U.S. Army Chemical Corps. By 1966, munitions capable of delivering BZ had been stockpiled and stored in military depots. In recent years, however, these have been dismantled and the contents destroyed. At the present time, incapacitating munitions are no longer in our armamentarium.

POSSIBLE APPROACHES TO INCAPACITATION

Virtually every imaginable chemical technique for producing military incapacitation has been tried at some time. Between 1953 and 1973, at the predecessor laboratories to what is now the U.S. Army Medical Research Institute of Chemical Defense, many of these were discussed and, when deemed feasible, systematically tested. Chemicals whose predominant effects were in the central nervous system were of primary interest and received the most intensive study. But other substances capable of disrupting military performance were also investigated, including some biological toxins. Nor were chemical agents and toxins the only possibilities considered; other candidates included noise, microwaves, light, and foul odors.

Nonchemical Agents

Physical disturbances (including loud noises, microwaves, and high-intensity light) and substances capable of causing intense sensory stimulation are among the nonchemical methods explored to impair performance.

Noise

Devices to produce loud or unpleasant sounds were built and, in some cases, were tested fairly extensively. Various sound patterns, including white noise and high frequencies, were tried. Although the sounds produced were annoying, they were relatively ineffective unless used at intensities that were either impractical to deliver over a large area or too likely to cause permanent hearing impairment.

It is interesting to note that the blare of trumpets has been used in battle throughout history to demoralize or confuse enemy forces. In addition, journalists reported that irritating rock-and-roll music was played during Operation Just Cause, the 1989 mission to Panama that resulted in the capture of Panamanian President Manuel Noriega. Similar loud music was played by the U.S. Treasury Department's Alcohol, Firearms, and Tobacco team for the same purpose during the siege of the Branch Davidians in 1993 at Waco, Texas.

Microwave Bombardment

Microwave effects on the central nervous system were investigated (in laboratory animals) beginning in the late 1960s. Consideration was given to the possibility of using a microwave generator to produce military incapacitation. Concern about long-term adverse effects, however, caused this idea to be abandoned.

High-Intensity Photostimulation

Light sources of high intensity, adjusted to oscillate at frequencies that theoretically might impair visual perception and concentration were also studied for a short period, but this approach was ulti-

mately judged to be impractical and probably unsafe (ie, it could cause retinal damage).

Olfactory Assault

Even the concept of olfactory incapacitating agents was briefly explored. Various obnoxious odors, including those produced by skatole derivatives, were found to be highly aversive, possibly sufficiently to impair performance. However, the relative ease of protecting against such odors (eg, wearing masks) and the probability that a highly motivated enemy would not be appreciably deterred by aversive odors alone caused this line of investigation (which was never very popular with the research team) to be abandoned.

Chemical and Biological Warfare Agents

A variety of chemicals—most of them known before 1950 and usually grouped with the chemical warfare agents—produce incapacitation through physiological rather than psychological effects. This category is included in this historical review of incapacitating agents only for the sake of completeness; each agent is discussed in detail in a separate chapter in this textbook.

Likewise, a number of noninfectious biological agents (eg, the staphylococcal enterotoxins) can cause severe malaise and other systemic symptoms, which would severely impair the ability to fight. The same is true of sublethal doses of organophosphates (cholinesterase inhibitors) such as VX or GB. None of these systemic agents are acceptable for use as incapacitating agents because of their unacceptable safety margins (ie, the ratio of the lethal to the incapacitating dose).

Vesicants

The vesicants, which include such substances as mustard, produce painful burns of the skin and respiratory tract. These chemical warfare agents were used extensively during World War I, with disastrous consequences. They have been used by some Third World nations, however, in the recent past. Similarly, phosgene and chlorine are generally not used. Although all vesicants can certainly incapacitate, they also often produce death and extreme suffering. (For further discussion, see Chapter 7, Vesicants.)

Irritants and Nausea-Producing Agents

Irritant agents, including lacrimators (such as CN, the original tear gas, and CS, its more potent successor), are generally fairly effective and safe when properly used. Their drawbacks are twofold: (1) their duration of action is relatively brief (adaptation to the chemical insult usually occurs after less than 30 min of continuous exposure) and (2) highly motivated individuals can fight through (ie, ignore) their effects. Thus, agents of this type would be relatively ineffective against dispersed, well-trained troops.

Nausea-producing agents (eg, DM) may have substantial effectiveness but they can be toxic. Highly potent relatives of apomorphine (a well-known emetic) are known but they have rather low safety margins. (For further discussion of CN, CS, and DM, see Chapter 12, Riot Control Agents.)

Psychochemical Agents

Virtually all drugs whose most prominent effects are psychological or behavioral (sometimes referred to as psychochemicals) can be classified into four fairly discrete categories: stimulants, depressants, pyschedelics, and deliriants. These drugs all can cross the blood–brain barrier with ease, and they exert their most dramatic effects on the central nervous system. Their interference with higher functions (as opposed to basic vegetative functions, which are primarily under brainstem control) are of greatest relevance to the goal of producing military incapacitation. The higher functions of the brain (attention, orientation, perception, memory, motivation, conceptual thinking, planning, and judgment) are more easily disrupted than are the more robust systems that regulate the physiological functions that are essential to life. Thus, it is possible to disable intelligent behavior at doses much lower than those that might have a direct lethal effect.

Stimulants

Stimulants include amphetamines, cocaine, caffeine, nicotine, and epileptogenic substances such as strychnine and metrazole. Some phenethylamines (among which the amphetamines are perhaps the best known) have additional effects that can best be classified as "psychedelic" and will be discussed below. None of the conventional stimulants appears to have sufficient potency to be usable as an airborne incapacitating agent, and low doses could even prove counterproductive, since moderate stimulation might easily lead to a soldier's more energetic and aggressive performance. Amphetamines, in fact, have successfully

been employed to offset fatigue and enhance cognitive function.

Depressants

A large variety of compounds come under the heading of depressants, but none holds much promise as a practical incapacitating agent. Barbiturates generally require doses of several hundred milligrams to produce heavy sedation. For example, 200 mg of secobarbital was found to produce a decline of only about 20% in a 25-trial, time-reproduction task[14]; other studies have produced similar results. Morphine and other opioids could be incapacitating, and very potent analogs (eg, etorphine) have been synthesized,[15] but the lethal dose is only 10- to 20-fold greater than the incapacitating dose.

The more potent antipsychotic (neuroleptic) major tranquilizers such as haloperidol and other butyrophenones often produce relatively little sedation, although they reduce hyperactivity. Their tendency to produce extrapyramidal symptoms such as acute dystonia is an additional liability, and their potency, although considerable, generally would not satisfy logistical constraints. The minor tranquilizers would be virtually useless because of their relatively mild effects and limited potency.

Psychedelics

The psychedelic group includes D-lysergic acid diethylamide (LSD-25) as its most well known member. LSD was, in fact, a drug of great interest to the military (as well as the whole nation) for many years starting in the early 1950s. Systematic testing of LSD as a possible incapacitating agent was done mostly between 1959 and 1965. Although highly potent (capable of producing complete incapacitation after oral doses of approximately 2.5 µg/kg), LSD tends to produce unpredictable (although well-coordinated) behavior. Affected individuals usually cannot carry out a series of instructions or concentrate on a complex task, but might be capable of isolated, impulsive actions such as firing a weapon accurately enough to be dangerous. Studies[16] conducted in simulated military settings demonstrated conclusively that even well-trained units become totally disorganized following total oral doses of less than 200 µg. Phenothiazines and benzodiazepines provide partial antidote effects, but there is no known complete antagonist.

The term psychedelic means "mind-manifesting" and refers to the alleged opening up and expansion of awareness that early clinicians attributed to LSD.

This led to its popularity for many years as a psychotherapeutic agent (or as an adjunct to therapy). The flood of ideas and images released by LSD accounts for its disorganizing effects; for example, soldiers under the influence of LSD would find it impossible to carry out an assigned task because of distracting, sometimes amusing, thoughts.

When administered by the aerosol route, using a particle size of approximately 5 µm, the ID_{50} (ie, the dose that incapacitates 50% of the exposed population; this dose is retained in the lungs and is available for absorption) was estimated to be 5.6 µg/kg, approximately twice the ID_{50} by the parenteral route.[17]

LSD analogs are numerous, but none exceed it in potency. Several other naturally occurring psychedelics (structurally related to LSD in that they contain an indole ring) are known. Psilocybin, ibogaine, and harmine are examples, but none of these shares the potency of LSD. Studies in several species of animals have shown that the lethal dose is at least 1,000-fold greater than the incapacitating dose. On the other hand, a single, intramuscular dose of 297 mg (about 100 µg/kg) caused sudden death in an elephant tested in the Lincoln Park Zoo in Oklahoma City, Oklahoma.[18] In humans, doses above 10 µg/kg have occasionally produced grand mal seizures,[19] although in recreational users, ingestion of as much as 50 µg/kg without serious consequences has also been observed.[20]

Although substituted indoles were apparently the only known synthetic psychedelic drugs prior to 1955, compounds with psychedelic properties have since been produced by making appropriate additions to the phenethylamine skeleton (the nuclear constituent of dopamine and norepinephrine). They include 3,4-methylenedioxymethylamphetamine (MDMA), the drug popularly known as "ecstasy." This and a number of related synthesized compounds[21] share many of the properties of LSD in that they induce an alteration of consciousness with startling perceptual changes that range from frightening to fascinating, depending on the user, his mental set, and the setting in which the drugs are taken. Some are very potent, but the same caveats that apply to LSD apply to their use in a military situation.

Phencyclidine (PCP) and the related compound ketamine have a mixture of clinical effects that reflects their complex pharmacology. Although acting on a specific subset of serotonin-type (HT-2) receptors in the forebrain,[22] PCP also has affinity for cholinergic, opiate, and dopamine receptors. This may explain PCP's ability to produce subjec-

tive changes ranging from euphoria to terror, as well as the apparent analgesia and "superman" effects described by police officers who have tried to arrest individuals under its influence. It was concluded quite early that PCP was not a suitable drug for military use, after its effects were observed in a few volunteers.

Deliriants

The fourth major group of psychoactive drugs can usefully be described as the deliriants. This category includes compounds that in small doses may produce clinically useful effects but in doses a few times larger produce delirium. Delirium is an incapacitating syndrome, involving confusion, hallucinosis, disorganized speech and behavior, as well as other features that will be described in greater detail below. Many drugs (and a number of metabolic alterations caused by disease states) can produce delirium. In their classic 1935 monograph, Wolff and Curran[23] enumerated more than 100 distinct etiologies of delirium. Many other drugs, some of them recently synthesized, could be added to that list. From this large number of possibilities, chemical compounds in a single subgroup—the "anticholinergics"—are regarded as most likely to be used as military incapacitating agents.

THE ANTICHOLINERGICS AS CANDIDATE INCAPACITATING AGENTS

"Anticholinergics" is the term generally used to refer to drugs that block the muscarinic effects of acetylcholine, in either the peripheral or the central nervous system. The best known are atropine and scopolamine, which are derived from solanaceous plants such as Jimson weed. Of course, many drugs in large overdose can produce delirium: tricyclic antidepressants, antihistamines, barbiturates, and phencyclidine are a few examples. But the anticholinergic BZ and a few structurally close synthetic relatives are the only ones known to be capable of producing delirium at very low dosage with a high safety margin—apart from scopolamine, which is one third as potent as BZ. A detailed discussion of BZ, and the nature of the delirium it produces, follows.

General Characteristics of Anticholinergics

The term anticholinergic as used in the context of this discussion refers more specifically to compounds that selectively block the brain's muscarinic receptor (now known to consist of several subtypes). Atropine (hyoscyamine) and scopolamine (hyoscine) are the most familiar medicinal anticholinergics. Historically, they were obtained from of the botanical family Solanaceae, which includes Jimson (or loco) weed, mandrake root, henbane, belladonna, and nightshade. Atropine and scopolamine are esters of tropic acid and contain a tertiary nitrogen moiety. This gives them the ability to cross the blood–brain barrier and block central muscarinic cholinergic receptors by competitive inhibition with acetylcholine, the natural neurotransmitter at these sites.

With regard to central activity, scopolamine is about 7-fold more potent than atropine but is shorter acting. An injection of as little as 1.5 mg of scopolamine hydrobromide is sufficient to cause the average 70-kg soldier to become delirious (and thus incapacitated) for 2 to 4 hours. Ten to twelve milligrams of atropine sulfate produces a similar effect, lasting 4 to 8 hours. In the peripheral cholinergic nervous system, both drugs produce parasympathetic blockade, causing tachycardia, elevation of blood pressure, hyperthermia (through blockade of sweat production), decrease in salivation, and reduction of gastrointestinal and urinary tract functions.

Impairment of near vision, attributable to a mixture of central and peripheral actions, is due to loss of accommodation (owing to ciliary muscle paralysis) and reduced depth of field (owing to pupillary enlargement). Alteration of skeletal muscle reflexes and tonus is related to central influences on the Renshaw interneurons in the spinal cord. Interaction between peripheral and central effects of anticholinergic drugs at different times following administration can cause biphasic changes in such parameters as heart rate and peripheral spinal reflexes. For example, heart rate may be slowed initially due to brainstem influences, after which vagal blockade tends to predominate, causing tachycardia. Similarly, knee and ankle reflexes may be exaggerated at first, but later are reduced. The pharmacokinetics that govern speed of distribution to the various drug compartments probably explain these biphasic phenomena. Although these variations in effects may seem to be academic distinctions, medical officers need to be aware of them when attempting to diagnose anticholinergic drug intoxication (which is discussed later in this chapter).

The above general characterization of anticholinergic drug effects produced by the familiar medications atropine and scopolamine also applies quite

well to a number of synthetic anticholinergic compounds. Many of these compounds are more potent than atropine or scopolamine. In some cases, their duration of action is quite short and in other cases much longer than either atropine or scopolamine; furthermore, a few display even greater preferential central activity than scopolamine. Some synthetic agents[24] can cause delirium with little or no change in heart rate or other of the signs of peripheral muscarinic blockade.

The degree of preferential affinity for various muscarinic cholinergic receptors in brain, heart, and smooth muscle probably explains the relative lethality of the various anticholinergics.[25] For example, estimated potency of five different anticholinergics in man based on heart rate is closely correlated with their relative lethality in the rat,[26] suggesting that death at high doses is probably due to cardiotoxicity. Previously, central toxicity was considered to be the cause of death from atropine. For humans, the dose that is lethal to 50% of the exposed population (LD_{50}) has been estimated to be about 100 mg.[27] However, using data from numerous reports of lethality and survival from high doses of atropine after reviewing more than 1,000 cases, Goodman calculated, using probit analysis,[28] the LD_{50} to be 453 mg (95% confidence level: 335–612 mg).

Combining these two analyses allows us to estimate the safety margin of various anticholinergics in humans. For BZ and atropine, the ID_{50} is approximately 40-fold lower than the LD_{50}; for scopolamine and other more centrally potent anticholinergics, the ID_{50} is approximately 100-fold lower than the LD_{50}. Computer models of dose distribution (using "Monte Carlo" statistical techniques) could perhaps use these dose ratios to help predict the probable number of lethalities (eg, if 50% of the target population were to be incapacitated by a particular agent, using a particular delivery system in a particular field situation). Clearly, however, this calculation would not be highly reliable.

The Most Likely Candidate: BZ or a Related Glycolate
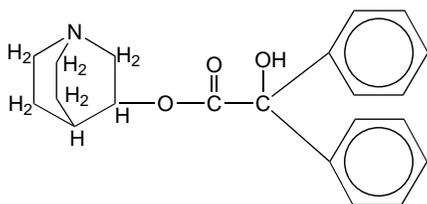
BZ

BZ was first experimentally studied for therapy of gastrointestinal diseases. However, reports were received of confusion and hallucinations, suggesting that even small excesses of dosage were likely to cause problems. BZ was quickly withdrawn from commercial study and turned over to the U.S. Army as a drug of possible interest as an incapacitating agent.

Structurally, BZ is 3-quinuclidinyl benzilate, today known to neuropharmacologists as QNB, a research standard for measuring central antimuscarinic activity.[29,30] The code name BZ is probably derived from benzilate, a molecular member of the larger chemical family known as glycolates (glycolic acid esters). BZ is a stable (environmentally persistent), crystalline solid, which makes it suitable for dissemination by heat-producing (thermal) munitions.

Clinical Pharmacology of BZ

BZ's clinical profile closely resembles that of atropine, differing significantly only in duration of action and potency. Whereas the ID_{50} of atropine (as free base) is approximately 140 µg/kg (8–14 mg per soldier), the ID_{50} for BZ is only 6.2 µg/kg (roughly 0.5 mg per soldier).[31] Although BZ is roughly 25-fold more potent centrally than atropine, BZ is only 3-fold more potent than scopolamine. This distinction is often not appreciated by nonpharmacologists, and BZ erroneously gained the reputation as an exceptionally potent and dangerous drug—not only in the popular press but also in scientific publications. As a result, regulations were issued by the U.S. Army Chemical Corps prohibiting the transport of even a few milligrams of BZ (or any related agent of similar potency) aboard a commercial airline!

Unlike the much-shorter-acting scopolamine, BZ's effectiveness by the oral route of administration is about 80% that of the intravenous or intramuscular routes (which are virtually identical). By inhalation, if disseminated at an optimal particle size (diameter about 1.0 µm), BZ is approximately 40% to 50% as effective as it is by injection. When applied to the skin dissolved in propylene glycol (a common vehicle for transdermal administration), apparent absorption is only 5% to 10% and the effects are delayed approximately 24 hours. (This is surprising since historical treatises suggest that belladonna drugs are readily absorbed from poultices.[31])

MED_{50} is defined as the dose that is minimally effective for mild cognitive impairment in 50% of

the exposed population; it produces mild impairment (25% decrease) in Number Facility (NF) performance.[32] The MED_{50} for BZ is approximately 2.5 µg/kg.[33] Recovery from this dose occurs within 24 hours. As stated above, the ID_{50} for BZ is 6.2 µg/kg and is defined as a persistent drop in performance on the NF to below 10% of baseline.

The effects of BZ by any route are slow in onset and long in duration. Performance decline is usually barely measurable at 1 hour, reaches a peak at about 8 hours, and subsides gradually over the next 48 to 72 hours. The duration of incapacitation (defined as the period during which NF performance remains below 25% of baseline) is approximately 24 hours at the ID_{50}. Doubling the dose produces incapacitation within 1 hour and prolongs recovery by approximately 48 hours. The effects of higher doses in humans are not known but would presumably occur even more rapidly and last considerably longer. In a field situation, wide variations in dosage would occur and mathematical models have been used to calculate the results under various conditions, but these can only give approximate predictions.

Anticholinergic Delirium Produced by BZ

As mentioned earlier, delirium is a nonspecific syndrome. Prior to the systematic study of anticholinergic delirium, however, correlation of the clinical features of delirium with performance of cognitive and other tasks under controlled conditions had not been accomplished. In the following discussion, aspects of delirium produced by anticholinergic agents will be described in relation to associated impairment in performance of various scoreable tasks of military relevance.

Following the administration of BZ at the MED_{50}, delirium appears in its mildest form, represented by a drowsy state, with occasional lapses of attention and slight difficulty following complex instructions. Moderate delirium (following doses of about 4 µg/kg) generally is manifested by somnolence or mild stupor, indistinct speech, poor coordination, and a generalized slowing in thought process, with some confusion and perplexity.

Individuals receiving the ID_{50} or higher almost always develop the full syndrome of delirium. There is surprisingly little variation among individuals when anticholinergics are given. Perhaps this is because these drugs operate more directly on the "hardware" of the brain—neuronal systems where "all-or-none" activity is more characteristic. Drugs such as LSD or the amphetamines, for example, act on serotonin or dopamine systems. These are modulatory rather than discrete in their actions; that is, their effects may vary in accordance with the prevailing mood, arousal, and motivational state of the subject.

When delirium is present in its full-blown state, the individual seems to be in a "waking dream," often staring and muttering, sometimes shouting, as simple items in the environment are variably perceived as elaborate structures, animals, or people. These hallucinations may arise from some trivial aspect of the surroundings, such as a strip of molding, a pillow, or an irregular spot on the floor. A total lack of insight generally surrounds these misperceptions.

Another striking characteristic of delirium is its fluctuation from moment to moment, with occasional lucid intervals and appropriate responses. An individual might answer "Shakespeare" when asked who wrote *Hamlet,* but when asked the same question 5 minutes later, might get down on the floor and attempt to remove an imaginary manhole cover, or become absorbed in a miniature World Series game being played out before his eyes.

"Phantom" behaviors, such as plucking or picking at the air or at garments, is characteristic (whence the old term "woolgathering"). This "carphologia," as it was known in the 19th century, can be comical at times. When two individuals are both delirious they may play off of each other's imaginings. A subject was once observed to mumble, "Gotta cigarette?" and when his companion held out an invisible pack, he followed with, "S'okay, don't wanna take your last one."

Recovery from drug-induced delirium is gradual, with a duration presumably determined by the pharmacokinetic persistence of the causative agent. The more spectacular and florid hallucinations are gradually replaced by more modest distortions in perception. (Instead of large animals, mice and insects are described by the subject.) Awareness gradually returns and with it comes the subject's partial insight that his mental faculties are not what they should be. Ironically, paranoid tendencies often emerge at this stage, as the individual senses that something is amiss but cannot carry out the reality testing required to rule out malevolent manipulation of the environment by others. A period of restorative sleep generally precedes the return to normal cognitive function.

DIAGNOSIS OF INCAPACITATING AGENT SYNDROMES

There is little likelihood that incapacitating agents other than anticholinergics would be used on the battlefield. They are the only type known to be at all practical, as discussed earlier. Furthermore, most potential enemies on today's horizon seem to have little inclination to use weapons of great subtlety or ones that are designed to minimize lethality. There seems little probability that reversible incapacitating agents would even exist in their arsenals.

Nonetheless, in view of the elusive maladies reported following Agent Orange exposure in the Vietnam War and the so-called "Persian Gulf War syndrome," it is important that medical officers be able to recognize chemical intoxication if it should occur, lest impaired performance be inappropriately attributed to stress, lack of motivation, or psychiatric illness. Fortunately, the effects of most anticholinergic agents are usually easily recognized. Medical students were long taught the old medical adage

"dry as a bone, red as a beet, hot as a hare, and mad as a hatter" as a means of remembering belladonna poisoning. The most useful diagnostic features of anticholinergics, indoles, cannabinoids, and anxiety reactions, all which can be confused with the signs of incapacitating agents, are summarized in Table 11-1.

Depending on dosage and time elapsed following exposure, certain features may be more apparent. As mentioned earlier, peripheral symptoms of tachycardia, dryness of skin and mucous membranes, and moderately elevated blood pressure may be the most conspicuous signs during the first few hours. Incoordination, confusion, and slurred speech also appear early. Soon thereafter, mydriasis, stupor, and even coma may develop. If casualties are not examined until many hours have elapsed, peripheral cholinergic blockade may have largely subsided. Bizarre behavior (eg, groping, undressing, mumbling) with failure to respond to

TABLE 11-1

DIFFERENTIAL DIAGNOSIS FOR INCAPACITATING AGENTS

Sign or Symptom	Possible Etiology
Restlessness, dizziness, giddiness, failure to obey orders, confusion, erratic behavior, stumbling or staggering, vomiting	Anticholinergics, indoles, cannabinoids, anxiety reaction, other intoxications (such as alcohol, bromides, lead, barbiturates)
Dryness of mouth, tachycardia at rest, elevated temperature, flushed face, blurred vision, pupillary dilation, slurred or nonsensical speech, hallucinatory behavior, disrobing, mumbling, picking behavior, stupor, coma	Anticholinergics
Inappropriate smiling or laughing, irrational fear, distractibility, difficulty expressing self, perceptual distortions, labile increases in pupil size, heart rate, and blood pressure, stomach cramps and vomiting	Indoles (may mimic schizophrenic psychosis in some respects)
Euphoria, relaxation, day-dreaming, unconcerned attitude, easy laughter, hypotension and dizziness on sudden standing	Cannabinoids
Tremor, clinging or pleading, crying, clear answers, decrease in disturbance with reassurance, history of nervousness or immaturity, phobias, bodily disturbances such as blindness and paralysis	Anxiety reaction

Adapted from Departments of the Army, Navy, and Air Force, and Commandant, Marine Corps. *Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries.* Washington, DC: HQ: DA, DN, DAF, Commandant, MC; 22 Dec 95: 3–1. Field Manual 8-285, NAVMED P-5041, Air Force Joint Manual 44-149, Fleet Marine Force Manual 11-11.

commands or conversation may then be the most conspicuous feature.

As recovery begins, apparent normality may be punctuated by sudden paranoid attempts to escape, or fleeting but vivid hallucinations may impinge on seemingly intact mentation. This is a time when panic, with its well-known dangers, may suddenly develop; vigilance (including restraint, if necessary) may be medically needed.

As noted earlier, the synthetic glycolate anticholinergics (those that are known so far) vary tremendously in their potency and duration of action. Signs and symptoms may last as little as 2 hours or as long as several weeks. Also, unfortunately, some glycolates produce few or no peripheral antimuscarinic features at the low end of the incapacitating dose range. Even the pupils may not be greatly enlarged. Such agents may produce signs that are difficult to distinguish from naturally occurring psychoses, unless the observer is well versed in the distinctly different pattern of cognitive changes that are pathognomonic of delirium. The occurrence of behaviors such as phantom drinking or smoking, picking or groping behavior, nonsensical speech, random disrobing, and the inability to follow simple instructions should greatly assist in making the differential diagnosis in such cases.

Detecting the covert use of other agents (those not suitable for large-scale dissemination) requires some knowledge of the effects of LSD and other psychedelics. Since LSD is a stimulant and usually prevents sleep, medical officers should not expect to see drowsiness or sedation. Staring, enigmatic smiling, and unusual preoccupation with ordinary objects are not uncommon. Responses to commands may be superficially normal, but laughter may supervene, or insubordinate and oppositional behavior. There are no practical diagnostic tests (although a sensitive fluorometric method for quantitative detection of LSD is known,[34] and blood samples could be useful in making a definitive diagnosis at a later time).

Marijuana intoxication is common in areas where the drug is indigenous, and the presence of reddened conjunctivae, along with the insouciance and relaxed joviality that marijuana produces, should make the diagnosis obvious. There is little likelihood that purified THC (tetrahydracannabinol, the active component of cannabis) would be used in a general military setting. Testing of blood and urine could be used if there is a need for definitive proof of its presence, but such tests are not always feasible or available.

With regard to covert use of incapacitating agents, the differential diagnostic problem is no different from that encountered in emergency rooms, and standard textbooks and manuals provide adequate guidelines. The possibility that secret research might produce some highly potent, unfamiliar variant of a known psychoactive drug cannot, of course, be ruled out, and blood analysis would seem the only way to determine its presence and chemical structure. However, medical officers in the field will be unlikely to encounter casualties produced by totally unfamiliar chemical substances.

MEDICAL MANAGEMENT

BZ and Other Anticholinergics

Prior to the mid 1960s, standard pharmacological textbooks taught that no antidote was available for the reversal of delirium caused by belladonnoid drugs. In fact, however, such an antidote had been reported by Kleinwachter[35] in the German literature in 1864. He noted that a lump of sugar saturated with extract of the Calabar bean (a natural source of physostigmine) proved efficacious in restoring lucid mental function to a prisoner who had become disoriented after drinking tincture of belladonna, thinking it was alcohol. Apparently this serendipitous finding was overlooked by early 20th-century clinical pharmacologists.

Nevertheless, reports[36,37] of reversal by physostigmine of coma (produced by injected doses of atropine as high as 212 mg, as therapy for certain psychiatric disorders) reappeared during the 1950s. Once again, this useful finding apparently received little attention from mainstream clinicians. The fact that physostigmine had been largely replaced in clinical practice by neostigmine and pyridostigmine, neither of which has much central antimuscarinic activity, may account for this curious oversight.

In 1963, the usefulness of physostigmine as an antidote was once again reestablished during investigations of BZ's effects in volunteers.[31] In 1967, U.S. Army physicians published the first double-blind controlled study demonstrating the effectiveness of physostigmine in reversing scopolamine delirium.[38] Later, they reconfirmed this finding in studies[39] of atropine and Ditran (a mixture of two synthetic belladonnoid glycolates, no longer available, that had enjoyed brief popularity as a treatment for depression[40]). In the course of other military medical studies, the drug was also noted to reverse the de-

lirium produced by a variety of synthetic anticholinergic glycolates.[24,31,41–43] Similar findings were soon reported in civilian studies.[44] Deliria produced by overdose with other drugs possessing anticholinergic side effects, such as tricyclic antidepressants[45] and antihistamines (personal observation, J.S.K.), were also noted to be treatable with physostigmine.

When given by the intravenous route, a dose of 30 µg/kg of physostigmine was found in further military studies[46] to be quite effective in the reversal of a variety of anticholinergics, although 45 µg/kg was the initial dose needed to reverse more-severe effects of delirium. It is interesting that physostigmine has also been used and reported to be effective for morphine-induced respiratory depression; alcohol withdrawal; and the effects of heroin, diazepam, ketamine, and fentanyl. In these instances, its activity may be due to a general direct cholinergic arousal effect, rather than to the inhibition of cholinesterase.[47] Case reports have come from the director of the Rocky Mountain Poison Control Center, near Denver, Colorado,[48] and the use of physostigmine as an antidote was reviewed by the director of the Munich, Germany, Poison Control Center.[49]

Although doses of as little as 2 to 3 mg of physostigmine alone may cause nausea and other signs of cholinergic excess (eg, salivation, intestinal cramping, and diarrhea), an intramuscular dose of 4 mg is generally well tolerated without any side effects when given as an antagonist to belladonnoid intoxication. In more than 100 subjects treated by one of the authors (J.S.K.), the only side effects were transient fasciculations in the platysmal area in one subject, and transient nausea and vomiting in a few others. If physostigmine should be given in error when no anticholinergic is present, its effects can be reversed by intravenous or intramuscular administration of 1 to 2 mg of atropine. Rapid intravenous use of physostigmine is not recommended because, in some individuals, the bolus effect on cardiovascular receptors may cause cardiac arrhythmias or even cardiac arrest. Most of these untoward outcomes, however, have occurred in patients who were in poor general health or suffering from heart disease.

When in doubt as to diagnosis, an intramuscular test dose of 1 to 2 mg, repeated after 20 minutes if no effects are noted, is recommended. Once the diagnosis is established by a definite improvement in mental status, improvement can be sustained by repeating the treatment at intervals of 1 to 4 hours. Dosage and frequency should be dictated by clinical judgment. For example, after 30 to 60 minutes, heart rate will rise as the effects of physostigmine

wane, and intellectual acuity will fade. Mental status can easily be estimated by having the subject do serial subtraction by 7 or 3; or by asking him to repeat a sentence containing a name, location, occupation, and employer; or by asking him simple questions regarding time, place, and person.

A solution of physostigmine is best administered orally, mixed with fruit juice to mask its bitter taste. Administered parenterally, only two thirds as much drug would be required to produce the same effects. A publication[50] distributed within the U.S. Army Medical Department contains detailed directions on how to dilute the parenteral preparation for oral use. In a combat zone, the oral route may be the only practical method to treat large number of casualties, relying on technicians (or, if necessary, other soldiers who are unaffected) to give measured amounts at specified intervals. With skillful titering, performance close to preexposure levels can be maintained. If the situation requires only that the soldier be comfortable and manageable, it is better to use a more conservative approach (eg, 1–2 mg by intramuscular injection or 2–4 mg administered orally every 2 h).

Once a suitable level of reversal is achieved (after 3 to 4 doses), delirium caused by BZ or other long-acting glycolates will usually relapse to its untreated severity in about 6 hours. (Shorter-acting belladonnoids such as atropine and scopolamine may be cleared from the brain by that time and thus further treatment may not be required.) The value of physostigmine in restoring and maintaining normal performance in a soldier given an incapacitating dose of BZ is illustrated in Figure 11-1.[51]

In another study, a single individual was given 6.4 mg of BZ intramuscularly and treated with a placebo; he was totally unable to perform simple arithmetic (the NF test) for approximately 48 hours. On a second occasion 14 days later, he was given the same dose of BZ and treated with a total of more than 200 mg of physostigmine over a 72-hour period without apparent ill effect. Not only could he perform at levels close to his baseline, but he generally felt normal and could eat, play pool, and read without difficulty as long as treatment was continued.[31]

For reasons that are not fully understood, physostigmine is relatively ineffective if given during the first 4 to 6 hours following the onset of BZ effects. Physostigmine is likewise ineffective if given earlier than 45 minutes following administration of the shorter-acting scopolamine.[38] Also, use of the antagonist does seem to not shorten the duration of the underlying intoxication; in fact, if treatment is not maintained, recovery from intoxication may
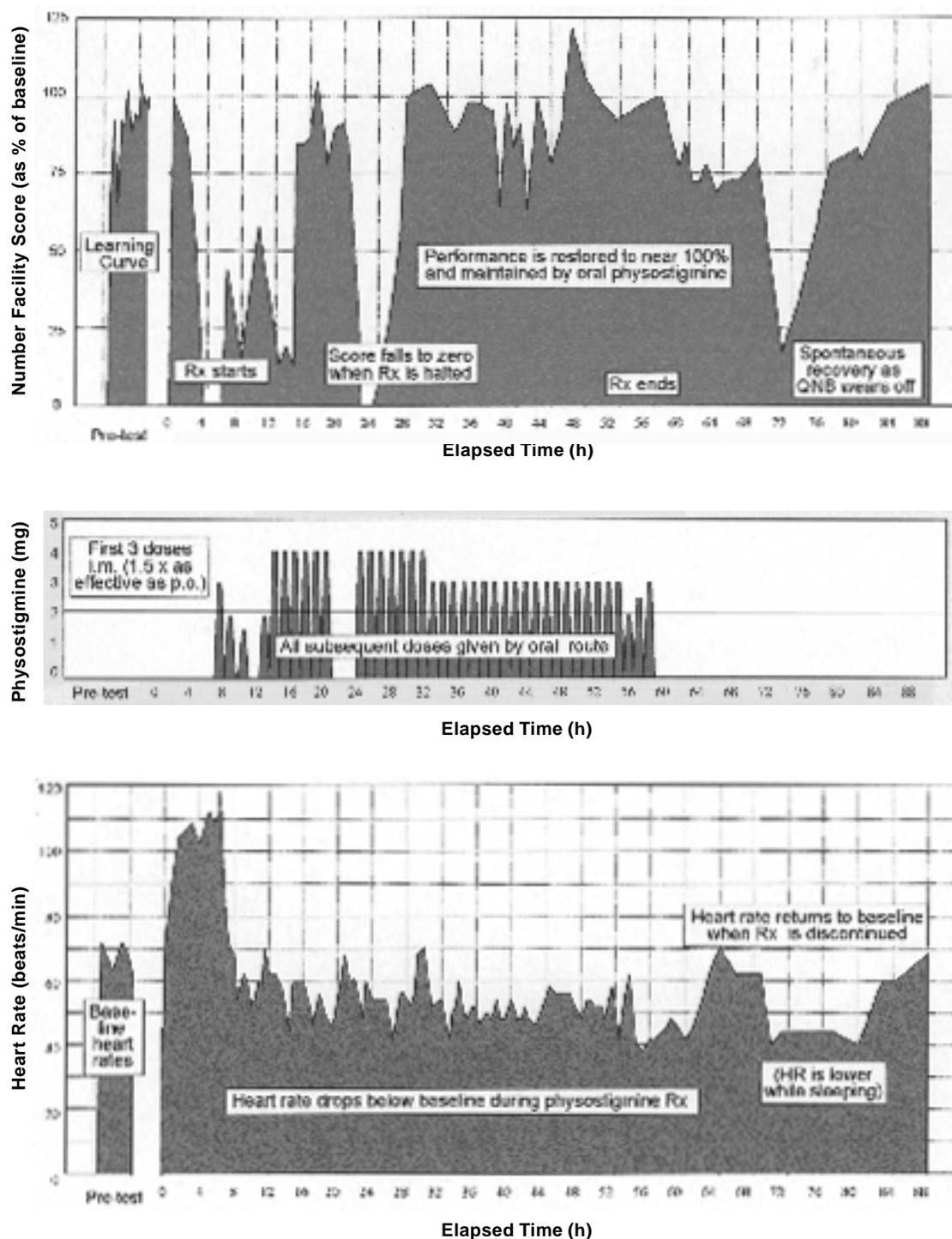
Fig. 11-1. The effectiveness of physostigmine in the treatment of 3-quinuclidinyl benzilate (QNB) intoxication. The three graphs above are the summary record of Number Facility performance, top, and heart rate (HR), bottom, in a single volunteer after the administration of QNB (the Rx), center. An aerosol dose (particle size < 1.0 μm) of approximately 7.5 μg/kg (120% of the incapacitating dose) was administered via the inhalational route. Treatment with physostigmine was begun 6 hours after aerosol exposure (peak impairment occurs at 6–10 h). Without treatment, recovery from an incapacitating dose of QNB is gradual, requiring 72 to 96 hours. The effectiveness of physostigmine is evident. Adapted from Ketchum JS, Tharp B, Crowell E, Sawhill D, Vancil M. *The Human Assessment of BZ Disseminated Under Field Conditions*. Edgewood Arsenal, Md; 1967. Edgewood Arsenal Technical Report 4140.

be slightly prolonged.[31] Unknown pharmacokinetic or metabolic factors may underlie these curious phenomena. The practical implication, in any case, is that the treatment team should not be discouraged if early administration of physostigmine fails to bring about immediate, dramatic improvement.

Whether or not physostigmine is a fielded drug and therefore available to medical officers in deployable hospitals, ancillary supportive measures for such signs and symptoms of delirium as disorientation, hyperthermia, decreased salivation, and self-inflicted injuries to the skin are important, as is evacuation to an appropriate hospital (Exhibit 11-2).

As pharmacologists know well, physostigmine is an acetyl (or "true") cholinesterase inhibitor and, as discussed above, is an effective antagonist to cholinergic blocking compounds. A simplistic view of this phenomenon is that the excess acetylcholine created by the inhibition of the enzyme might antagonize (overcome) the effects of the blocker. The nerve agent VX, also an acetylcholinesterase inhibitor, has also been used successfully in the reversal of BZ.[52] Pseudocholinesterase inhibitors, such as

diisopropyl fluorophosphate (DFP), are less effective.[39] Tetrahydroaminoacridine (THA, also called tacrine), currently approved for use in senile dementia, Alzheimer's type, is also primarily a pseudocholinesterase inhibitor. In four subjects, 200 mg of oral THA was administered as an antagonist against BZ and proved moderately effective.[31] It was noted, however, to cause temporary changes in hepatic function tests and therefore was abandoned.

Physostigmine is probably not as highly regarded as it was during the 1970s and 1980s, when it was given to patients with a variety of intoxications, often without a rational indication. On the other hand, physostigmine is probably not as dangerous as current thinking and textbooks would indicate. It has predictable effects, and there are specific indications for its use. A drug with such potent vagal blocking activity probably should not, as mentioned earlier, be given rapidly by the intravenous route (risking a sudden bolus effect on cardiovascular receptors), since it is almost equally effective when given intramuscularly. The brief delay in absorption will rarely make a significant difference.

EXHIBIT 11-2

ANCILLARY SUPPORTIVE MEASURES FOR THE TREATMENT OF DELIRIUM

1. Control and containment are of primary concern since delirium can easily lead to accidents and inadvertent injury to others. Comatose or stuporous casualties may emerge from immobility into a stage of persistent crawling or attempted climbing (primitive behaviors sometimes called "progresso ostinato" [obstinate progression] in 19th-century descriptions of delirium). It is better to tether or otherwise loosely restrain individuals who are disoriented than to let them move about freely without close supervision.

2. The danger of hyperthermia must be considered if the environment is warmer than 75°F. Death from relatively low doses of anticholinergics has occurred due to impairment of sweating. Wet cloth is effective to reduce body temperature, and the casualty should be placed in the shade, if available.

3. Dryness of the mouth and parching of the lips should be managed with moist swabs and small amounts of vaseline or unguents. Hard candy may induce sufficient salivation to keep the tongue moist. Fluids should be given sparingly and food withheld until the individual is obviously capable of normal chewing and swallowing.

4. Significant skin abrasions can be caused by persistent repetitive movements, especially against rough surfaces. The use of wrappings or gloves may be useful. A tendency to remove clothing is common, and reflects a general regression to simple habitual behaviors. If the environment is harsh, the casualty's clothing may have to be secured so it cannot be removed.

5. Evacuation from the field to more adequate medical facilities is desirable in most cases. If not possible, separation of affected individuals into small groups (eg, in tents) is preferable to large aggregations, where a few confused and hyperactive individuals can lead to an escalating problem of crowd control.

If administered by the intravenous route, a dose of 30 µg/kg (about 2 mg in a 70- to 75-kg person) is quite effective in reducing peripheral effects such as tachycardia and hypertension; higher doses (at least 45 µg/kg) are usually needed to significantly reverse the more-severe central cognitive effects.[46] Again, this route of administration should be used with great caution in patients who are already receiving other drugs that predispose to convulsions or cardiac arrhythmias.[53] If in doubt, medical officers might consider trying a small (≤ 1 mg) test dose before administering fully effective quantities. This amount will not generally completely reverse the central nervous system signs but may give detectable indications that the antidote is effective. Furthermore, a dose this small will not adversely affect the average adult who has not been exposed to an anticholinergic compound.

LSD, Other Indoles, and Phenethylamine Derivatives

In the unlikely scenario where psychedelic compounds such as LSD or one of the more potent phenethylamine analogs are encountered on the battlefield, depressant drugs are useful, even if suboptimal, antidotes. For many years, chlorpromazine (Thorazine, manufactured by SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.) was the preferred treatment of "bad trips" caused by LSD. Only moderate (although dose-related) improvement in performance was demonstrated in our laboratories when a 50- to 100-µg/kg dose of Thorazine was administered orally, 60 minutes following intravenous administration of 2 µg/kg of LSD.[54] More recently, the short-acting benzodiazepines, such as lorazepam (Ativan, manufactured by Wyeth-Ayerst Laboratories, Philadelphia, Pa.), have been widely used to good effect. Surprisingly, a leading clinical psychopharmacologist[55] recommended barbiturates to one of the authors (J.S.K.) during a recorded interview, on the grounds that LSD was a highly effective antagonist to barbiturates in laboratory studies. To our knowledge, this suggestion has not systematically been tested in humans.

Opioids

The treatment of opioid overdose is well established. Naloxone (Narcan, manufactured by Du Pont Multi-Source Products, Garden City, N. Y.) in doses of 0.4 to 1.0 mg has been recommended,[56] and is the standard treatment in most emergency rooms. Naloxone can be given subcutaneously or, if the soldier appears to be deeply comatose with severely depressed respirations, by the intravenous route. Repeated injections at intervals as short as 30 to 60 minutes are usually required in the presence of a large overdose to prevent relapse into coma with a possibly fatal outcome.

SUMMARY

Incapacitating agents, capable of temporarily preventing military personnel from performing their duties (without permanent injury), have a long and colorful history. For a variety of reasons, they have not generally been used in overt warfare in the 20th century. Preference for conventional lethal weapons by most aggressors, and the many uncertainties applying to their use by friendly nations, have led to their elimination from the United States's arsenal. However, in the attempt to find an incapacitating agent that would meet the numerous constraints imposed by practical and political concerns, many studies were conducted, especially by the U.S. Army, during the 1960s. Although an ideal incapacitating agent was never found, much was learned from the search.

Of all known psychochemical options, anticholinergics appear to be the most feasible for military use. 3-Quinuclidinyl benzilate (BZ) or a related potent glycolate seem to be the most likely candidates among the many that have been studied. Following an absorbed dose of less than 1 mg, BZ produces an acute brain syndrome, best described as delirium, that lasts 2 to 3 days.

Reversal of the effects of BZ by physostigmine and other anticholinesterase agents has been clearly demonstrated to be both effective and safe when properly used in otherwise healthy individuals. The benefits and methods of use of physostigmine were brought to the attention of modern medicine by U.S. Army medical officers, who conducted these studies.

Incapacitation produced by less likely candidates such as LSD and other indole derivatives, psychedelic phenethylamines, and potent opioids is theoretically possible, but it is unlikely that any of these compounds would be employed militarily. Covert use, which is logistically easier to accomplish and has fewer constraints, opens a broader spectrum of possibilities. This, however, is a concept that involves considerations that generally extend beyond the scope of chemical warfare.

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