Chapter 12

INCAPACITATING AGENTS

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INTRODUCTION

In 600 BCE, soldiers of the Greek king Solon induced debilitating diarrhea in enemy troops by throwing highly poisonous hellebore roots into streams supplying their water. Today, scientists seeking new nonlethal incapacitating substances are studying neuropeptides and neuromodulators. Both then and now, the goal has been to weaken an enemy without the use of lethal force. In the last half-century, "incapacitating agent" has become the accepted military term for such unconventional weapons.

According to the US Department of Defense, an incapacitating chemical agent falls into the more general category of nonlethal weapons (NLWs) and therefore shares the following characteristics:

> [Non-lethal weapons] are explicitly designed and primarily employed so as to incapacitate personnel or materiel, while minimizing fatalities, permanent injuries to personnel, and undesired damage to property and the environment.
> Unlike conventional lethal weapons that destroy their targets principally through blast, penetration and fragmentation, non-lethal weapons only employ means other than gross physical destruction to prevent the target from functioning.
> Non-lethal weapons are intended to have one, or both, of the following characteristics:
>
> 1. They have relatively reversible effects on personnel or materiel.
> 2. They affect objects differently within their area of influence.[1]

Use of an incapacitating agent by conventional military forces would face political, military, medical, and budgetary constraints. Factors such as effectiveness, relative lack of toxicity or excessive persistence, logistical feasibility, predictability of behavior, manageability of casualties, availability of antidotes, limitations imposed by treaties, and cost would need to be considered. No proposed incapacitating agent has yet been acceptable.[2] Further considerations would come into play before any decision to deploy an agent. Methods and equipment must be designed to manufacture, store, and transport the agent. Troops in the field would require extensive training to operate what might be a complex delivery system. Medical personnel would need to learn how best to treat the casualties, working within the confines of the battlefield.

This chapter reviews the properties of many possible chemical incapacitating agents, as well as a few that are physical in nature, and their diagnosis, treatment, and general principles of management.

HISTORY AND MODERN DEVELOPMENT

Although few references to the historical use of drugs for military purposes appear in contemporary publications, a substantial literature describes a variety of tactical efforts to incapacitate enemy forces with mind-altering chemicals. The rarity of new publications about the incapacitating chemical agents considered most promising can be attributed in part to the exponential acceleration of pharmaceutical discovery, which has eclipsed interest in many drugs used widely in the past. In addition, computerized databases tend to include only research reports published since 1970. Consequently, the current focus is on new drugs tailored to specific nervous system targets. The "new age" neurochemicals under consideration are not new—they incorporate advances in neuropharmacology but no new modes of action; some are even less practical than those proposed in the 1960s. Even the agents attracting interest in the 1960s were not as new as they seemed.

In 1961 Ephraim Goodman, a psychologist in the Edgewood Medical Laboratories, Maryland, systematically reviewed 100 years of reports and letters appearing in four leading American and British medical journals (as well as a more limited number of several respected German medical periodicals). Goodman discovered numerous reports of deliberate administration, particularly of atropine and related drugs, to produce "behavioral toxicity" (a term introduced by Joseph Brady in 1956). Often, these substances were used by single individuals, but some can be considered examples of drugs used as "weapons of mass destruction" or "mass casualty weapons." The following excerpts from Goodman's review show that incapacitating agents are not a new approach to military conflict:

> According to Sextus Julius Frontinus, Maharbal, an officer in Hannibal's army about 200 BCE, …. 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.[3]

His review continues, "Another example of the use of atropinic plants for military purposes occurred during the reign of Duncan, the 84th king of Scotland (1034–1040 CE), who used wine dosed with 'sleepy nightshade' against the troops of Sweno, king of Norway."[4–6] Goodman also reports:

> During his assault in 1672 on the city of Groningen, the Bishop of Muenster tried to use grenades and projectiles containing belladonna against the defenders. 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.[5]

Goodman adds another incident, "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."[7] Finally, in reference to more recent use:

> 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 a 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."[8,9]

The international community, particularly in the latter half of the 20th century, has repeatedly tried to find ways to make warfare more humane. Remorse and indignation were widely expressed following the use during World War I of such weapons as chlorine, mustard, and phosgene, which killed or injured hundreds of thousands of soldiers in European trenches. One consequence of these outcries was an international ban on chemical weapons adopted by the Geneva Convention in 1925.[10] The United States, although not a signatory to this document until 1975, strongly supported its purpose.

Although no chemical weapons were used during World War II, the German military had developed and stockpiled several lethal organophosphate nerve agents, which were never deployed. The Allies learned later that Hitler had a morbid fear of poisonous chemicals, having been temporarily blinded by a British gas shell in World War I; furthermore, the Nazis erroneously assumed that the Allies were in possession of the same lethal compounds and would retaliate in kind.[11]

Agents of lower lethality were used against terrorists in the 2002 Moscow theater incident (see further discussion below), reducing the potential number of deaths by more than 80%. Claims that BZ (or a related incapacitating agent) was used against defenseless civilians fleeing the Serbian genocidal purge in 1999 are difficult to confirm but considered to be true. Widespread reports of hallucinations implicate an agent related to BZ. A less credible claim by Alistair Hay,[12] although supported by the testimony of many witnesses and casualties, mentioned features uncharacteristic of BZ.

Another unsubstantiated assertion is the claim by Dr Wouter Basson, a South African political figure with a reputation for falsehoods, to having proof that BZ was used in Iraq during the Persian Gulf War.[13] His description of victims as "wide-eyed and drooling" is incongruent with the marked dryness of the mouth produced by BZ and other anticholinergic agents—proof of popular misperceptions about the pharmacological qualities of BZ and its chemical relatives.

A seemingly novel concept—using psychochemicals to produce temporary ineffectiveness—was unintentionally given credibility by Albert Hofmann's report that lysergic acid diethylamide (LSD), one of a series of ergot derivatives he had synthesized in 1938, possessed incredibly potent mind-altering effects. Hofmann realized this when he accidentally ingested an undetectable amount in 1943, while replicating the synthesis of some of his 1938 compounds. He then deliberately ingested a presumably subthreshold amount of the contents of bottle number 25 (hence, "LSD-25") and experienced a bizarre and at times terrifying "trip."[14]

LSD-25 arrived in the United States in 1949, when psychiatrist Max Rinkel brought a sample from Sandoz Pharmaceuticals in Switzerland and began work with Dr Paul Hoch at the Boston Psychopathic Hospital. Dr Harold Abramson, a New York chemist, allergist, and psychotherapist, began studying the clinical characterization of the fascinating new drug.[15] Over the next 2 decades Abramson published numerous reports describing LSD's unique effects on perception, mood, and cognitive activity. His dose/response approach quickly stimulated wider testing. Soon LSD became a

multipurpose drug, used in psychiatric hospitals either to treat schizophrenics or to produce "model psychoses" in normal volunteers.[16] The Central Intelligence Agency also became involved with LSD beginning in 1951,[17] leading to serious damage to the agency's reputation when the use was uncovered during several 1977 Congressional investigations.

The head of the US Army Chemical Corps, Major General William Creasy, recognized the military potential of LSD. Creasy persuaded Congress[18] that LSD could quickly disable an enemy force, yet not destroy lives, describing a floating cloud of LSD that could disable everyone in the area for several hours without serious aftereffects. Creasy stated that the Soviet Union was spending 10 times as much as the United States on chemical weapons research and was no doubt already using LSD in covert operations. He recommended tripling the funding of Chemical Corps research and development, especially for evaluation of the military potential of LSD as an NLW. This request was endorsed by an almost unanimous vote, leading to an elaborate incapacitating agent research program.

LSD testing by both civilian contractors and at Edgewood Arsenal, Maryland (1955–1960), showed LSD's effects to be disturbingly unpredictable. However, military testing continued from 1961 to 1966 to complete LSD's characterization by various routes, evaluate treatment methods, and develop a sensitive assay technique to aid in diagnosis. Just as LSD testing was ending, the Edgewood program was reinvigorated by Hoffmann-LaRoche, Inc, who gave the Chemical Corps permission to study its patented compound, 3-quinuclidinyl benzilate.[19] (A similar "incapacitating agent" was deployed by the Soviet Union even before 1960. In 1959, the Soviets attempted to poison 1,248 employees of Radio Free Europe, covertly mixing atropine with table salt in the cafeteria. A US agent foiled the plan.[20,21]) The Edgewood program received additional support under the "blue skies" policy, first announced by President Eisenhower and later supported by President Kennedy, which brought many new personnel and funding for facilities and equipment.

POSSIBLE METHODS OF INCAPACITATION

Nonchemical Methods

After considering virtually every possible chemical technique for producing military incapacitation, and rejecting many as too toxic or unmanageable, investigators at the Edgewood Arsenal clinical laboratories examined dozens of potentially disabling but reasonably safe substances between 1953 and 1973. Although drugs that predominantly affected the central nervous system soon became of primary interest and received the most intensive study, development of nonchemical devices and techniques, protective garments, and antidotes to existing agents, as well as physician training for medical management of agent effects, were important objectives as well.

Nonpharmacological materials and techniques potentially capable of reducing an enemy's military competence were also developed in related programs that continued after volunteer testing of chemical agents was terminated in 1973. The most significant of these developments are listed below.

Auditory Methods

Several devices that produce loud or unpleasant sounds have been designed, but most have not been tested in volunteers, and none have been deployed. Some critics consider incapacitation produced by directed sound energy devices to be inhumane because none can be guaranteed not to produce injury.[22,23](Because they involve nonmedical systems, these devices will not be further discussed in this chapter.)

Microwave Devices

In the late 1960s several animal studies of microwave effects produced reversible incapacitation.[24]

Use of Light

Another proposed incapacitation modality uses high-intensity photostimulation adjusted to oscillate at certain frequencies calibrated to impair visual perception and concentration.[25] Laser light in the ultraviolet spectrum gained brief interest, but was soon judged impractical, and further light use has not been pursued.

Olfactory Devices

The notion of producing incapacitation through "olfactory assault" was briefly explored in the 1960s. Various obnoxious odors, such as those produced by derivatives of skatole (an excretory chemical) were initially thought aversive enough to impair military performance. Obnoxious odors have actually been tried as tactical weapons, but their effectiveness remains in doubt because masks that attenuate such odors would reduce

their impact. Furthermore, a highly motivated soldier might not be appreciably deterred by aversive odors alone. Such considerations halted this line of investigation at Edgewood Arsenal. Research in this area was later resumed, however, and a few programs exploring the effectiveness of malodorous substances are still active.[26]

Nonlethal Mines

Incapacitating mines such as taser mines and modular land mines are examples of NLWs.[27]

Armed Robots

A group of robots capable of intelligent mobility under the control of sophisticated algorithms, armed with sublethal weapons, could act in concert as a patrolling unit. Current international humanitarian law contains very little to govern the behavior of autonomous nonhuman devices. Robots offer real promise but are not yet sufficiently advanced or dependable to be deployed.[28]

A wide range of other immobilizing devices are appearing on the market, some of which could deliver chemicals, paralyzing electric shocks, or nonlethal chemicals. However, they also carry hazards such as the risk of asphyxiation[29] (see further discussion below).

Chemical Methods

The list of possible chemical incapacitating agents has become long. Relatively unattractive for military use are those that alter a victim's physical integrity, possibly producing irreversible injury. Less objectionable are those that temporarily disturb some physiological or biochemical function. Their effects usually remit without residual disability after periods varying from minutes to months. Some agents in this latter category can be attenuated or even reversed with the help of antidotes.

Chemicals that produce injury are part of a diverse group of pharmacological agents that alter mental competence. These chemicals may affect mood or motivation, or they may interrupt the ability to process information and respond appropriately to events in the environment. "Psychochemical" is a useful term for these agents, although most of the medical community calls them "psychoactive drugs."

Psychoactivity is manifested by a variety of subgroups in the pharmacological family. The "psychoactive" umbrella covers many familiar therapeutic drugs such as stimulants, sedatives, analgesics, psychedelics, tranquilizers, and centrally active anticholinergic medications. In small doses, these drugs are useful in the treatment of either physical maladies or mental disorders. In doses greatly above therapeutic values, however, they produce incapacitation.

The safety margin or therapeutic index of psychochemicals varies greatly, as does the quantity of each required to impair the ability to function. All psychochemicals cross the blood–brain barrier with ease; some take up residence in the brain for only a few minutes or hours, whereas others are more persistent, clinging to brain receptors for days or even weeks with or without treatment. Although none of their effects is permanent at sublethal doses, at very high multiples of the incapacitating dose they can be lethal (as can any drug). Although basic concepts of drug action are familiar to physicians and pharmacologists, from a military standpoint, variations in potency, duration, safety, and mode of action require defined criteria to assess their suitability as incapacitating weapons. The following sections examine 14 categories of chemical agents, both peripheral-acting and psychochemical. The text will summarize data developed through clinical testing whenever such information is available.

A drug's mode of action is a key factor that greatly influences the decision whether or not to explore it further. Drugs that affect behavior indirectly by some aversive somatic effect, even if relatively safe, tend to be least reliable. Drugs that affect brain function directly tend to be more useful, as long as they do not compromise life-sustaining systems. Sometimes referred to as basic vegetative functions, life-sustaining systems are mostly under the control of mechanisms located in the lower brain stem or in the midbrain, which have developed phylogenetically as the most essential brain areas. These areas regulate respiration, blood pressure, body temperature, and many instinctual or well-learned reflexes.

The drugs of greatest military interest are those that tend to affect predominantly "higher integrative" or "cognitive" functions, which process sensory data or conscious decision-making, including attention, orientation, perception, memory, and motivation. Working together, these capabilities regulate conceptual thinking, planning, and judgment. These functions depend on complicated neural networks and are thus more vulnerable and easily disrupted than are basic vegetative functions. These drugs are rarely devoid of some effect on basic autonomic mechanisms, but ideally such effects are tangential to the drug's main action—impairment of the higher integrative systems. Effects on systems essential to life are side effects compared to effects on thoughts, feelings, and the anticipatory "programming" of behavior (planning).

Nerve Agents

Although lethal chemicals such as sarin or VX are not usually considered incapacitating drugs, cholinesterase inhibition can produce severe incapacitation through neuropsychological effects alone, independent of such easily recognized bodily effects as miosis, respiratory distress, muscular weakness, autonomic disturbances, and general malaise. Sarin and VX are relatively reversible; some of the other cholinesterase inhibitors are much longer acting.

A chemical worker at Edgewood Arsenal, accidentally exposed to GD (soman), provided an example of the effects of a persistent anticholinesterase agent. After receiving emergency treatment, he spent several weeks under close observation with the usual supportive measures and repeated doses of atropine and other therapeutic agents.[30] In addition to the usual life-threatening effects on respiration, cardiovascular activity, and muscle strength, all of which were reversed with atropine and 2-pralidoxime chloride, his performance of standards continued to be impaired even after his physical signs and symptoms had largely subsided.

This case of accidental poisoning presented a unique opportunity to follow the time course of GD's central nervous system effects. Through daily psychological testing the medical staff could measure the quantitative aspects of cognitive impairment produced by cholinergic excess in the brain. Of considerable interest was the greater reversal of the patient's cognitive deficits by small doses of scopolamine than by doses of atropine equivalent in peripheral potency. Scopolamine was also more effective in reducing the frequency and severity of nightmares, a common central effect of nerve agents. Recovery was gradual and took several weeks, as GD-inactivated cholinesterase was slowly replaced by newly generated, functionally normal enzyme.[30]

In a study of Australian gardeners, mental defects developed in the absence of significant peripheral physiological changes. These workers had been exposed daily to seemingly unremarkable concentrations of organophosphate pesticides. Although acute effects did not occur, the frequent, sometimes prolonged exposure to the chemicals produced cumulative effects on mental function. Hallucinations occurred and changes in cognitive efficiency became increasingly apparent, even though the men appeared otherwise normal.[31]

Irritants, Nausea-Producing Agents, and Toxins

Irritants and nauseants, including lacrimators such as CN (the original tear gas), CS (successor of CN), and DM (a nauseant) are incapacitating and generally safe when properly used.[32] These agents have the following two qualities: (1) Their duration of action is short, because adaptation to the irritant effects usually occurs after 30 minutes or less of continuous exposure, with rapid recovery when the atmosphere clears; and (2) highly motivated individuals can sometimes "fight through" their effects.

Vesicants

The vesicating agents, which include such substances as mustard, produce severe incapacitation by burning the skin and respiratory tract.[33] Vesicants have been internationally condemned, and although some nations have used them in past decades, the probability of their use solely as an incapacitant in today's conflicts is low because they have no impact on mental function.

Indole-Based Psychedelics

"Psychedelic," a term coined by Humphry Osmond in collaboration with Aldous Huxley in 1957, means "mind-manifesting" and refers to the alleged expansion of awareness that early users thought to be a unique feature of LSD and related compounds.[34] Its ability to bring forth repressed memories, fears, and fantasies supposedly made LSD a useful adjunct to traditional psychoanalysis, although few practicing psychiatrists felt comfortable using it in their practice, for the effects could be explosive and difficult to control in a doctor's office. The unmanageable flood of ideas, images, and emotions that LSD unleashes accounts for many of its disorganizing effects. A person under the influence of incapacitating doses of LSD would find it impossible to carry out complex tasks because of the sensory overload of frightening or perplexing thoughts, accompanied by a kaleidoscope of rapidly changing perceptions and emotions.[35,36]

Although many psychedelic drugs have been extracted from plants, or synthesized in the laboratory, LSD was undoubtedly the best known of these indole-based psychedelic drugs. It gained attention from diverse subcultures and scientists starting in the mid-1940s (long before it was tested systematically at the Edgewood Arsenal for possible military usefulness).[37] Chemical Corps testing of LSD as a possible incapacitating agent began in the mid 1950s.[38] When administered to volunteers, LSD produced virtually complete incapacitation. For unexplained reasons, the drug was less effective when given by the oral route than when inhaled.[39] As previously reported by civilian investigators, LSD produces bizarre and unpredictable but often well-coordinated behaviors. Individuals given larger doses usually cannot carry

out a series of instructions or concentrate on a complex task. Most of the volunteers expressed the belief, moreover, that they might tend to perform unpredictable, impulsive actions.[40]

Phenothiazines and benzodiazepines have frequently been used to ameliorate LSD intoxication. One of the nation's leading psychopharmacologists, George Aghajanian, however, suggested that barbiturates would be his choice as an LSD countermeasure, based on his studies showing the effectiveness of LSD in reversing the action of barbiturates.[41] Nevertheless, an injectable benzodiazepine such as lorazepam (Ativan, Baxter Healthcare Corp, Deerfield, Ill) combined with "talking down" is now the most commonly accepted therapeutic approach.

Aghajanian has spent 5 decades studying the mode of action of LSD. Based on his findings, it seems probable that the lack of a specific antagonist to LSD's effects is attributable to its complex action.[42] LSD has affinity for several subtypes of serotonin receptor, with additional effects on locus coeruleus (alerting) neurons in the brainstem and specific glutamate (stimulating) receptors in the neocortex. Recently Aghajanian collected evidence indicating that some glutamate-producing cells in the forebrain are overstimulated by LSD, leading to a functional state of "hyperfrontality."[43] Excess glutamate "spills over" into spaces between cells and apparently impinges on adjacent neurons that subserve normally separated modalities. This may explain the synaesthesia described by some LSD-intoxicated persons, whereby specific musical notes produce specific color sensations, or numbers become associated with particular tastes or odors (less common).[42]

Before 1963 no reliable quantitative assay of LSD blood levels was available. Blood levels were assumed by many pharmacologists, relying on LSD's known half-life of 20 minutes in rats. Two possible explanations were offered for the much longer clinical effects in human subjects: either (1) the drug triggered some unusual brain activity that continued after the drug had left the body, or (2) some of it became "sequestered" in the brain, where it continued to disrupt normal neuronal activity. Aghajanian and Oscar Bing, while assigned to the Clinical Research Department at Edgewood, laid these speculations to rest in 1964 by developing a sensitive spectrophotofluorometric assay for blood levels of LSD (then one of the most fluorescent drugs known). They found the that blood elimination time of LSD was approximately 175 minutes, resolving the discrepancy between the 8- to 12-hour duration of its effect and the earlier estimates of approximately 20 minutes. Cognitive performance, using the 3-minute number facility (NF) test, revealed a striking parallelism between scores and blood levels[44] (ruling out the idea that LSD was somehow retained in the brain even after disappearing completely from the blood). A second retrospective study on the respiratory route of administration of LSD estimated that the approximate time for blood elimination was about 160 minutes. Military scientists did test administration of LSD by the oral route, but they were more interested in the effectiveness of the respiratory route.[45]

LSD analogs are numerous and vary in duration of action, but none exceeds it in potency. Many are naturally occurring psychedelics structurally related to LSD and well known to ethnopharmacologists (specialists in indigenous drug-containing plants). LSD is remarkably safe from a toxicity standpoint. Studies in several species of animals have shown that the lethal dose is at least 1,000-fold greater than the incapacitating dose.[45] An exception was the sudden death of an elephant in the Oklahoma City, Oklahoma, Lincoln Park Zoo during behavioral experiments following a dose of LSD.[46] This accidental overdose was later attributed to the rapid absorption of the injected dose (delivered by dart), creating a bolus effect that resulted in significant laryngeal spasm with subsequent asphyxiation; it probably also overwhelmed the elephant's heart.

Physiological effects of LSD are unremarkable, consisting mainly of peripheral adrenergic symptoms such as tachycardia, mildly elevated blood pressure, slight hyperthermia, and an average increase of about 2 mm in pupil diameter. Doses above certain amounts have occasionally produced grand mal seizures,[47,48] although some European recreational users claim to have ingested larger amounts without serious consequences.[49]

In the 1960s chlorpromazine (Thorazine, Smith Kline & French Laboratories, Philadelphia, Pa) was the most widely used drug to help subjects "come down" from the intense symptoms produced by LSD. However, no systematic test had determined whether chlorpromazine was a true antagonist or merely a "quieting" agent. Aghajanian and Bing explored chlorpromazine's ability to reverse performance decrements by conducting a double-blind study at clinically used dose levels to modulate LSD's effects and evaluating volunteer cognitive function using the NF test.[50] Although scores rose modestly for about 4 hours, the duration of LSD effects was not shortened. Benzodiazepines such as lorazepam, which is short-acting and injectable, have since become the preferred drugs for easing LSD effects.[51] Benzodiazepines are also nonspecific in their tranquilizing actions.

Because of the unpredictable nature of its effects, LSD was removed from consideration as a military incapacitating agent. Volunteer testing of the drug ended in 1966, after the government categorized it as

a class I drug, making it illegal to use without a special research permit.

Phenethylamine-Based Psychedelics

Mescaline, derived from the peyote cactus, has long been valued for its psychedelic properties, and is legal for ceremonial use in certain Native American tribes. Unlike LSD, it is a substituted phenethylamine and thus a structural relative of norepinephrine and dopamine. Numerous synthetic relatives of mescaline with psychedelic properties exist, including 3, 4-methylene-dioxymethylamphetamine (MDMA), the drug popularly known as ecstasy. MDMA and related synthetic compounds induce dramatic alterations of consciousness similar to the effects of LSD.[52,53] Startling perceptual changes that range from frightening to enlightening can occur, depending on the user and the setting in which the drug is taken.

Some phenethylamine psychedelics are very potent, but the same limitations as with LSD apply to their use in a military situation. The potent phenethylamine derivatives were not tested in Edgewood volunteers, except for a small dose of a relatively potent amphetamine derivative given to four people.[52,53] No significant changes in performance were observed.

Cannabinoids

For a short period the Chemical Corps became interested in a potent extract of marijuana known as "red oil."[54] In 1961 oral doses were given to 12 volunteers. The dose-response regression curve had a low slope, and few of the classical cannabis effects were observed, except in one subject. Modest decrements in standardized arithmetic and word recognition tests occurred. For political as well pharmacological reasons, however, the effort was dropped, particularly after members of the press ridiculed the idea of the Army using an illegal recreational drug as a weapon of war.[55] It appears unlikely that a cannabinoid will be used as an incapacitating agent in the foreseeable future.

Stimulants

Included in this category are cocaine, caffeine, nicotine, and the unsubstituted amphetamines, as well as epileptogenic substances such as strychnine and metrazole.[56] All of these stimulants, except for the last two, increase alertness and may actually enhance performance in some tasks. At high doses D-amphetamine produces psychotic symptoms such as paranoia, and illusions develop in 50% of normal subjects. The hyperactivity produced by stimulants would probably be an undesirable effect in most situations. This group has little to offer as incapacitating agents.[57]

Sedative Hypnotics

A large variety of compounds fall under this heading, but none hold much promise as a practical agent. Barbiturates, for example, generally require doses of several hundred milligrams to produce heavy sedation. In a trial limited to four volunteers who received secobarbital (Seconal, Eli Lilly, Indianapolis, Ind), the drug caused only a 20% decline in the performance of a sensitive time-reproduction task.[58] Many civilian studies have yielded comparable results. The low safety margin of barbiturates is well known (they are frequently used for suicide attempts). As incapacitants, they probably have no useful military role.

Opioids

Originally derived from the poppy, these venerable drugs, of which morphine is the prototype, have only recently regained interest as potential incapacitating agents. Candace Pert and Solomon Snyder first isolated and characterized the morphine (μ) receptor in 1972.[58] Subsequently, δ (delta), κ (kappa), and σ (sigma) receptors were identified. The σ-receptor is no longer considered a pure opioid receptor, but is also a target of the dissociative anesthetic best known as PCP (phencyclidine).[59] The μ-receptor subserves analgesia, but also inhibits respiration.

The treatment of opioid overdose is well established. Naloxone (Narcan, Endo Pharmaceuticals, Chadds Ford, Pa) in doses of 0.4 to 1.0 mg has been the standard treatment in most emergency rooms for many years.[60,61] The antidote can be given by the intramuscular route, but if the subject appears to be deeply comatose with severely depressed respirations, it should be given by the intravenous route. Repeated injections at intervals as short as 30 to 60 minutes are usually required in the case of a large overdose to prevent relapse into coma and a possibly fatal outcome.

The morphine antagonist nalorphine (naloxone) has affinity for the κ-receptor. It also produces analgesic effects in its own right. Pentazocine (Talwin, Sanofi-Aventis, Bridgewater, NJ) is active at the κ-receptor, producing analgesia, but is dysphoric in opioid-naive subjects. However, some users have become addicted to pentazocine and are tolerant to its unpleasant effects. The role of the δ-receptor, originally isolated from the rat vas deferens, has antinociceptive, seizuregenic, and convulsive properties. It may have a role in depression. The three major opioid receptors interact in a complex manner, the details of which are beyond the scope of

this chapter.

During the Cold War (1945–1991), a great deal of research was directed to chemicals that were not necessarily lethal but would incapacitate enemy personnel. The United States and the former Soviet Union, in particular, investigated a wide number of pharmacological agents for their potential as incapacitants, such as depressants, hallucinogens, belladonna drugs, and opiate derivatives.[62] The relatively recent development of several highly potent opioids is potentially significant for military use. Fentanyl, the first of these new opioids, is many times more potent than morphine. Super-potent derivatives of fentanyl have since appeared and might be used to produce incapacitation.

Since 1996 a number of different analogs of fentanyl have been introduced for use in anesthesia; the best known are carfentanil, sufentanil, and remifentanil. Their pharmacological activity is similar to that of other opiates; consequently, they produce all of the effects of heroin, including analgesia, euphoria, miosis, and respiratory depression. Because of their high lipid solubility, regardless of the route of administration, the fentanyls reach the brain very quickly, thus providing a very fast onset of action. This quality led to their popularity as illicit drugs; they were initially unregulated as controlled substances, but this loophole has since been closed by the US Drug Enforcement Agency.[63]

Among the multiple opioid receptors,[64] μ-receptors mediate analgesia, euphoria, physical dependence, and depression of ventilation, whereas κ-receptors mediate sedation and diuresis. Drugs may act at more than one opiate receptor, with varying effects. Traditionally, narcotic antagonists such as naloxone and naltrexone have been used to reverse opioid agonists' effects.[65] Also, when used clinically, longer acting opioids such as fentanyl may produce renarcotization because of differences in the pharmacokinetics of agonists and antagonists.

Because fentanyl is not listed in any of the schedules of the 1993 Chemical Weapons Convention (CWC), and is traditionally characterized by the rapid onset and short duration of 15 to 30 minutes of analgesia, some people are arguing for it to be legally considered a riot control agent according to the definition set forth in the CWC.[62] On October 23, 2002, at least 129 of the almost 800 hostages held by Chechen terrorists in the Moscow Dubrovka Theatre Center died when Russian authorities pumped what many believe was fentanyl into the building.[66–68] Although the Russian authorities insisted that emergency personnel were prepared with 1,000 doses of antidote in anticipation of the raid, controversy continues over whether local hospitals and physicians were adequately informed about the gas prior to its use in the rescue operation.[69] According to some reports, a few Russian officials suggested that a mixture of fentanyl and halothane, as well as massive doses of carfentanil, were used to produce a fully incapacitating concentration inside the theater.[70]

Carfentanil, an even more potent opioid, is often used to rapidly immobilize large wild animals, as well as horses and goats.[71] This drug produces rapid catatonic immobilization, characterized by limb and neck hyperextension. Adverse effects include muscle rigidity, bradypnea, and oxygen desaturation.

Recycling and renarcotization have been reported as possible causes of death when low doses of antagonist are used. This occurs when the antagonist has a shorter duration than the opioid it reverses. To avoid this, the treating physician must ensure close observation and may need to administer additional doses of antagonist. Recent research suggests that selective stimulation of the 5-HT_{4a} serotonin receptor might be a way to reverse or prevent μ-receptor–induced respiratory depression.[72,73] This is because the 5-HT_{4a} receptor affects the intracellular concentration of cyclic adenosine monophosphate in respiration-regulating brainstem neurons in a manner opposite to the μ-receptor.[72] Numerous investigators are currently pursuing this promising line of research, hoping to separate the anesthetic from the respiratory effects of μ-agonists.

Following antagonist treatment, residual opioid may still be present at lethal levels, even when it has partially cleared the body. Although there were naloxone syringes found in the Dubrovka theater, it is also possible that the doses given were insufficient to reverse the respiratory depression.

Dissociative Anesthetics

PCP (Sernyl, Parke Davis and Co, Detroit, Mich), introduced as an anesthetic in the 1950s, has a unique combination of pharmacological properties never seen previously.[74] Without causing loss of consciousness or respiratory depression, it prevents awareness of surgical pain. For a time it was touted as an anesthetic breakthrough, but as subsequent reports of unnatural agitation and disruptive behavior began to accumulate, its use in adults was halted. Because it prevented respiratory problems, it continued to be used in children for short procedures, but it also produces delirium and frequently caused management problems.

PCP was subsequently designated for use only in veterinary surgery, where its subjective effects are evidently less of a problem. In its place, ketamine (Ketalar, Parke Davis and Co, Detroit, Mich), a short-acting chemical relative of PCP, proved more manageable clinically and became an acceptable anesthetic for certain surgical procedures in both humans and

animals.[75] Like PCP, its mode of action is complex. Also like LSD, both ketamine and PCP are attracted to 5-HT_{2A} serotonin receptors, but they also possess affinity for a number of other receptors. PCP acts as an inverse agonist at the glutamate receptor, which has been called "the PCP receptor."[76] PCP's multiplicity of receptor affinities produces a complex clinical picture, with psychedelic, delirium-producing, energizing, and analgesic elements.

Treatment for PCP, unlike for LSD, is difficult. Benzodiazepines are generally used. Physostigmine might improve cognitive functions, and antipsychotics are often given to minimize irrational behavior, but these alone do not reverse all effects. Keeping the patient in dark, quiet surroundings tends to minimize agitation and assaults. Temporary hospitalization may be necessary.[77,78]

Tranquilizers

Diazepam (Valium, Hoffmann-La Roche Inc, Nutley, NJ), successor to the popular drug meprobamate (Equanil, Wyeth-Ayerst Laboratories, Madison, NJ) was initially hailed as a wonder drug when it was introduced in 1959. Psychiatrists considered it to be a "minor tranquilizer," in contrast to "major" tranquilizers such as chlorpromazine or haloperidol (Haldol, Ortho-McNeil Pharmaceutical, Raritan, NJ). Over the next two decades, a bevy of benzodiazepines structurally related to diazepam appeared on the market.[79] The major tranquilizers were meanwhile renamed "antipsychotics," and the minor tranquilizers became "anxiolytics." In addition to their antianxiety and tranquilizing effects, benzodiazepines have muscle relaxant, anticonvulsant, amnestic, and sedative-hypnotic effects. All of these contribute to performance impairment.

Flumazenil, a benzodiazepine antagonist, is an inverse agonist at the γ-aminobutyric acid receptor with the side effect of severe anxiety[80] (which would obviously affect performance adversely, making it incapacitating in its own right). Many benzodiazepines now exist, ranging in duration of action from extremely short to very long. Some of the more recently introduced members of the family are also highly potent. Alprazolam (Xanax, Pfizer US Pharmaceuticals, New York, NY) and triazolam (Halcion, Pfizer US Pharmaceuticals, New York, NY) require small oral doses to produce sedation or tranquilization.[81]

Antipsychotic Drugs

The more potent antipsychotic drugs were previously called major tranquilizers or "neuroleptics." These drugs are valued not only for their sedative effects, but also for their ability to reduce psychotic hyperactivity. They tend to produce extrapyramidal symptoms similar to parkinsonism, which is caused by the loss of dopamine-producing neurons in the midbrain's substantia nigra. Because they block dopamine receptors, most antipsychotic drugs cause the same problems: rigidity, tremor, and reduced activity, which results in considerable impairment of movement. The potency of some antipsychotic drugs, although impressive, generally would not satisfy logistical constraints.[82] Performance decrements on the usual cognitive measures were only slightly dose related, with a shallow dose-response slope, meaning that the effects would be difficult to predict, and considerably higher doses would be required to ensure complete incapacitation.

The lethal dose of an antipsychotic drug is many times the therapeutic dose, but precise values are unavailable. Very high doses of haloperidol, for example, can be tolerated; paradoxically, such high doses may actually produce fewer parkinsonian side effects. Some clinicians, perhaps frustrated with the lack of response to ordinary doses of haloperidol, tried giving larger doses to psychotic patients. No greater therapeutic response occurred, but because haloperidol has significant anticholinergic effects at high doses, it prevented the parkinsonian side effects that are common after lower doses (working like the drug benztropine [Cogentin, Merck & Co Inc, Whitehouse Station, NJ]).[83] Malignant hyperthermia, a potentially lethal complication, occasionally occurs after repeated ingestion of much lower doses.

Parkinsonian symptoms, particularly in the form of painful spasms of neck muscles, occurred in many of the volunteers. These did not usually appear until 8 to 12 hours after ingestion, and invariably responded promptly to an injection of benztropine or diphenhydramine (Benadryl, Pfizer Consumer Healthcare, New York, NY). Delayed spasms could therefore be prevented in the field if prompt medical custody of the affected individuals were assured.

Neuropeptides and Neuromodulators

The newest potential incapacitating agents are those that operate on the central nervous system, either as surrogate neurotransmitters with unwanted effects, or as natural neuropeptide transmitters applied in ways that were unintended by nature. Military consideration of such substances was spurred by a review submitted in 2000 by the University of Pennsylvania under a government contract.[84] In 2003, three analysts from the US Defense Intelligence Agency authored a paper called

"Biotechnology: Impact on Biological Warfare and Biodefense."[85] They warned that weapons designers of the future will be able to engineer agents that produce a range of effects "…including death, incapacitation, neurological impairment." The former Soviet biological weapons effort, ostensibly halted as early as 1992, included programs to develop "bioregulators" as weapons to replace classical chemical weapons. Some chemical warfare watchers are very concerned about the growing interest in such substances. The following excerpts are illustrative:

> There is concern over the potential use of bioregulators as weapons in warfare or by terrorists. A paper in late 2001 stated that these organic compounds "… are capable of regulating a wide range of physiologic activities…" and if used as weapons "… could potentially cause profound systemic effects on multiple organ systems."[85(p3)]
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> . . .
>
> Bioregulators of concern discussed in the paper included cytokines, eicosanoids, neurotransmitters, hormones, and plasma proteases. Neurotransmitters mediate chemical transmission in the nervous system through their interactions with specific receptors. In the central nervous system these neurotransmitter-receptor interactions have a major role in regulating consciousness, mood, anxiety, perception, and cognition.[86]

Bioregulators have sometimes been referred to as "calmatives," and some writings list as calmatives compounds that do not produce this outcome. The term has also been used by the Russians in referring to the drug (or drugs) used in the Moscow theater rescue in 2002. Most therapeutic drugs that relieve anxiety or produce some kind of sedation, including anxiolytics such as diazepam, antipsychotic neuroleptics such as chlorpromazine, muscle relaxants, and sedative-hypnotic drugs have been placed in this artificial category.

Also included in the category are serotonin 5-HT_{1a} receptor agonists and selective serotonin reuptake inhibitors, of which fluoxetine (Prozac, Eli Lilly, Indianapolis, Ind) is perhaps the most familiar. A profusion of these "biochemical" antidepressants have emerged on the psychiatric market since Prozac was released in 1987. From a pharmacological standpoint, it seems inappropriate to call them calmatives. As antidepressants they tend to produce increased energy, even though initial use may sedate some patients, especially those suffering from insomnia. Their therapeutic effects may be delayed by days to weeks. They all possess high safety margins, but their potential effectiveness as incapacitating agents is questionable.

Some researchers suggest that α-2 adrenergic agonists should also be classified as calmatives. Clonidine, the most familiar drug of this type, is effective in very low dosage and used to lower blood pressure or to help in the stabilization of hyperactivity in children. Although potent and able to produce sedation, clonidine would be a highly dangerous drug to use in the field because life-threatening hypotension can develop after even small multiples of the therapeutic dose.

The opioids can also be found in the calmative category, as can exotic drugs such as D_3 dopamine agonists and cholecystokinin-B antagonists. Pramipaxole, a D_3 dopamine agonist, is useful in treating the symptoms of Parkinson's disease, and as little as 0.125 mg supposedly helps to control restless legs syndrome. It has also been used to treat compulsive gambling. Antagonists of cholecystokinin-B (the brain counterpart of the stomach hormone gastrin) can potentiate the analgesic effects of other drugs and lower body temperature under certain conditions. Corticotropin-releasing factor antagonist is a hypothalamic hormone. It stimulates the release of adrenocorticotropic hormone from the pituitary gland. How an antagonist to this hormone would serve any useful purpose as a calmative is unclear.

The calmatives group has come to include not only the neuropeptides and neuromodulators but many preexisting drug families long recognized by pharmacologists to be distinctly different in their effects. Often belladonnoid drugs (such as BZ) or scopolamine, formerly marketed as Sleep-Eze (Whitehall Laboratories, New York, NY), an over-the-counter bedtime sedative, are barely mentioned. Sleep-Eze was a popular drug among people with insomnia until it was taken off the market because of concerns about potential abuse. Sominex (JB Williams Company, Cranford, NJ), Sleep-Eze, and Unisom (Pfizer Consumer Healthcare, New York, NY) are now over-the-counter drugs containing diphenhydramine (an antihistamine) instead of scopolamine as their active ingredient. Both antihistamines and cannabinoids have also been ignored by the calmative classifiers.

From a purely practical standpoint, administering some of the candidates with larger molecules by aerosol, or even via ingested food or water, is difficult to imagine. Not only are many neuropeptides quite large, consisting of long chains of amino acids, but they would also be extremely difficult to disseminate in the field. Even if they reach the lungs or digestive tract, they would ultimately be obliged to cross the blood–brain barrier, a difficult task for many complex molecules.

Pharmaceutical companies are currently developing methods to ferry or "piggyback" hormones, antibodies

and other proteins, and large polypeptide molecules through the blood–brain barrier, but current technology can not surmount all the associated limitations of using such chemicals in a battlefield environment.[87] Nevertheless, according to Chapter V of the *Army Science and Technology Master Plan*, "…under investigation are protein carriers for transport of immunogenic peptides; vectored vaccines with multiple immunogenic properties; approaches to block the actions of threat agents on target receptor sites; and rapid evaluation of genetically altered microbes."[88] Such techniques may also be applicable to neuropeptide and neuromodulator incapacitating agents, but their relevance to field dissemination of calmatives is obscure.

Anticholinergic Deliriants

Anticholinergic deliriants, or "belladonnoids," have been and continue to be the category most likely to be considered for incapacitating agents. "Anticholinergics" is the term commonly used to refer to these drugs because their main action is to block both the central and peripheral muscarinic effects of acetylcholine. Belladonnoids are a subgroup of the anticholinergics that resemble atropine. This useful term, like opioids in the case of morphine-like compounds, refers not only to naturally occurring substances such as atropine and scopolamine, but also to synthetic glycolates that are actively antimuscarinic in the brain. Delirium is the syndrome resulting from doses of these drugs significantly above appropriate clinical doses.[89]

Many psychoactive drugs can produce delirium when given in high multiples of the therapeutic dose. In their classic 1935 monograph, Wolff and Curran enumerated more than 100 drugs and disease-altered metabolic states they had observed to produce delirium.[90] "Deliriants" as a drug category is a seemingly artificial but useful subdivision of chemical agents. It arises from the Latin "delire," meaning "to rave." By the very origin of the term, delirium is equivalent to incapacitation, because it combines confusion, hallucinosis, disorganized speech and behavior, and a variety of autonomic features.

Atropine and scopolamine are esters of tropic acid, which gives them the ability to cross the blood–brain barrier and block central cholinergic receptors of the muscarinic type by competitive inhibition of acetylcholine, the natural neurotransmitter at these sites.[91] Physician investigators at Edgewood found that scopolamine was about 7-fold stronger than atropine in terms of relative central potency. An injection of a very small amount of scopolamine hydrobromide, for example, is sufficient to produce 4 to 6 hours of incapacitating delirium in the average person. A larger dose of atropine sulfate produces a similar effect, but recovery requires 8 to 12 hours.[89,92]

In the peripheral cholinergic nervous system, both drugs cause parasympathetic blockade, resulting in tachycardia, elevation of blood pressure, hyperthermia (through blockade of sweat production), decrease in salivation, and reduction of gastrointestinal and excretory bladder functions. Impairment of near vision, attributable to a mixture of central and peripheral actions, also occurs due to loss of accommodation (from ciliary muscle paralysis) and reduced depth of field (from pupillary enlargement).

The interaction between peripheral and central effects of anticholinergic drugs at different times following administration sometimes causes biphasic changes in such variables as heart rate and peripheral spinal reflexes. For example, heart rate may be slowed initially because of brainstem influences, after which vagal blockade tends to predominate, causing tachycardia. Similarly, knee and ankle reflexes may be exaggerated at first, but are later reduced, a phenomenon mediated by Renshaw interneurons in the spinal cord. The pharmacokinetic principles 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 the differential diagnosis of incapacitation (discussed later in this chapter).

BZ. The most likely incapacitating belladonnoid, and the first studied synthetic example, is 3-quinuclidinyl benzilate, referred to as QNB by neuropharmacologists, but known as "BZ" to the Chemical Corps. This designation probably derives from its benzilate structure, although some people suggest that it comes from the "buzz" it supposedly produces. BZ is a stable glycolate, an environmentally persistent crystalline solid.

Clinical Pharmacology of BZ. BZ's clinical profile closely resembles that of atropine and scopolamine, differing significantly only in duration of action and potency.[93] BZ by the oral route of administration is about 80% as effective as by either the intravenous or intramuscular routes. When applied to the skin in propylene glycol or other appropriate solvent, however, apparent absorption is only 5% to 10%. Pilot studies of percutaneously administered BZ in dimethyl sulfoxide (a solvent vehicle that facilitates the passage of some drugs through the skin) showed a delay in peak effects by approximately 24 hours; contrary to historical treatises suggesting that belladonna drugs are readily absorbed from poultices.

Inhalation studies with BZ, both under laboratory

conditions and when administered in the open air under simulated field conditions, showed it to be approximately 60% as effective as when given orally or parenterally. When breathing is regulated at 1 L per breath, 15 breaths per minute (the typical volume of respiration for a moderately active soldier), approximately 80% of 1-μm aerosol particles (the optimal diameter) is retained by the lungs. Of this quantity about 75% is actually absorbed; the remainder is inactivated within the lung or bronchial lining.[93,94]

Most absorbed BZ is excreted via the urine after hepatic metabolic processing. Edgewood chemist Albert Kondritzer studied the brain distribution of BZ and found it to be eliminated in three stages, roughly in parallel with the clinical phases of BZ symptoms.[95] It appears to be most persistent in the hippocampus and other regions that control memory and cognitive functions.

BZ produces anticholinergic drug effects similar to those produced by atropine and scopolamine, as do many related synthetic belladonnoids. To make quantitative comparisons of the growing number of related compounds subjected to testing, it became necessary to establish operational definitions of such parameters as the minimal effective dose and the incapacitating dose, as well as onset time, duration, and other important attributes. After much discussion, the following definitions were adopted:

- Minimal effective dose: dose required to produce mild cognitive impairment in 50% of the exposed population. The threshold for a minimal effect is two successive scores below 75% of baseline performance on the NF test.[39]
- Incapacitating dose (ID_{50}): dose required to produce two successive scores below 10% of baseline (at which point incapacitation is clinically obvious).[93]
- Onset time: time of first NF score below 25% of baseline, which for BZ is approximately 4 hours.
- Partial recovery time: time at which two successive scores return to 25% or higher in subjects exposed to the ID_{50}.[94]
- Duration: number of hours between onset time and partial recovery time in subjects exposed to the ID_{50}.
- Peripheral potency: dose required to elevate heart rate to a maximum of at least 100 beats per minute. This heart rate was found to be the most reliable indicator of a significant peripheral anticholinergic effect, regardless of baseline heart rate.[94]
- Relative central potency: ratio of peripheral potency to ID_{50}. This ratio was found to be useful in estimating the median lethal dose (LD_{50}) of the belladonnoids, because peripheral potency (manifested by heart rate increase) at the incapacitating dose is a predictor of belladonnoid lethality.[96]

Other operational definitions include full recovery time (the percentage of patients returning to above 75% of baseline for cognitive testing using the NF test), prolongation time (increase in duration at double the ID_{50}), and dose-onset factor (degree to which onset time is shortened as a function of dose).

Features of BZ-Induced Delirium. Delirium is a nonspecific syndrome.[90] Before the systematic study of anticholinergic delirium, however, the clinical features of delirium had not been correlated with performance of cognitive and other tasks under controlled conditions. In the following discussion, aspects of delirium produced by anticholinergic agents will be described in relation to associated impairment in cognitive performance as measured by the facility test already described.

Following the administration of BZ at the minimum effective dose, delirium appears in its mildest form, represented by a drowsy state, with occasional lapses of attention and slight difficulty following complex instructions. Recovery is usually complete by 24 hours.

Moderate delirium generally is manifested by somnolence or mild stupor, indistinct speech, poor coordination, and a generalized slowing of thought processes, along with some confusion and perplexity. Although sluggish, the subject remains in contact with the environment most of the time, with occasional illusions but rarely true hallucinations. NF test scores decline by about 50%. Recovery occurs within 48 hours, and amnesia is minimal.

Individuals receiving the ID_{50} or higher usually develop the full syndrome of delirium. There is very little variation from person to person in their response to BZ (or other belladonnoids), perhaps 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, in contrast, act directly at specific serotonin and glutamate receptors and indirectly on others, including dopamine, norepinephrine, and opioid μ-receptors, with effects that vary in relation to the prevailing mood, arousal, and motivational state of the subject.

During the first few hours, subjects show increasing confusion but remain oriented. When delirium is present in its full-blown state, however, the individual

seems to be in a "waking dream," staring and muttering, sometimes shouting, as simple items in the environment are variably perceived as structures, animals, or people. These hallucinations may arise from some trivial aspect of the surroundings: a strip of floor molding has been called a strip of bacon; a bulky object led one subject to yell for help for an injured woman; and another described a Lilliputian baseball game on the rubber padding, evidently stimulated by uneven patches or shadows. A total lack of insight generally surrounds these misperceptions.

A striking characteristic of delirium is its fluctuation from moment to moment, with occasional lucid intervals during which appropriate answers are unexpectedly given to questions. Sometimes the correct answer gets temporarily shunted aside. An example of this unusual phenomenon was a subject who spouted gibberish when asked "who wrote Hamlet?" When asked where he lived a short time later, he answered, "Shakespeare." Phantom behaviors, such as plucking or picking at the air or at garments, are also characteristic. This behavior was termed "carphologia" in the 19th century. Sometimes two delirious individuals play off each other's imaginings. In one study one subject was observed to mumble, "Gotta cigarette?" and when his companion held out a nonexistent pack, he followed with, "S'okay, don't wanna take your last one."

Recovery from drug-induced delirium is gradual, the duration presumably paralleling the pharmacokinetic persistence of the causative agent. The more spectacular and florid hallucinations are gradually replaced by more modest distortions in perception. For example, illusions of large animals are replaced by those of smaller animals. As awareness of the time and place and recognition of people gradually returns, the subject enters a transitional phase during which he recognizes that his mental faculties are not what they should be, but suspects that something else is wrong. This may produce temporary paranoid delusions and withdrawal (or occasionally an attempt to escape from the room). A psychiatrist might be reminded of similar states observed in some schizophrenic patients.

During the period from onset of maximum effects until partial recovery at between 24 and 48 hours, the volunteers are completely unable to perform any task requiring comprehension and problem-solving. During this time and even during their gradual recovery, they are generally docile. Aggressive or assaultive behavior does not occur, except in the form of moments of irritability, sometimes punctuated by an attempted punch or other expression of annoyance. "Berserk" behavior or attack with an object is absent, contrary to some descriptions by those unfamiliar with the BZ delirious syndrome. Confusion may give way to panic in a few subjects as they near recovery, but this is always motivated by fear of imagined harm, and never by a desire to inflict severe bodily injury. Not once in several hundred drug-induced delirious states during the BZ studies was significant injury inflicted on the attending staff.

A period of restorative sleep generally precedes the return to normal cognitive function, accompanied by cheerful emotions. Many of the BZ subjects described a feeling of well-being following recovery. Initially, as reflected in their posttest write-ups, those who had been delirious can recall some events, but, as with dreams, their recollection soon fades. Thereafter, these fleeting memories are forgotten, in keeping with the clinical adage that delirium of all types is followed by amnesia.

Other glycolates. At least a dozen synthetic glycolates were provided to Edgewood Arsenal for testing in volunteer subjects. John Biel, at Lakeside Laboratories, Milwaukee, Wisconsin, prepared many of these compounds, making it possible to compare belladonnoid structures that differed only quantitatively in such parameters as potency, duration, speed of onset, and relative central potency.[96] His colleague, Leo Abood, was an early pioneer in the study of many of these compounds and formulated useful structure/activity relationships showing that duration and potency, for example, could be predicted from the position of particular features of the structure, such as the location of a hydroxyl moiety. Testing in volunteers validated many of these observations about structure. Abood's chapter in a National Academy of Sciences publication on chemical agents also contains a useful compilation of the number of volunteers tested at Edgewood Arsenal with each belladonnoid and a summary of the observed effects.[97]

Abood adds his personal knowledge of three graduate students who surreptitiously ingested up to 10 mg of BZ and were hospitalized. All three students had been in academic difficulty and had considered dropping out of school; however, after their recovery, their academic performance improved dramatically, and all went on to obtain PhDs and continue in gainful employment. In addition, several independent observers thought the students seemed happier and better adjusted. These unexpected changes tend to corroborate previous claims of psychiatric benefits from belladonna-induced coma therapy.[98–100]

Many synthetic belladonnoids were tested in the volunteers. Some of these were found to be more potent with fewer side effects, such as no significant increase in heart rate.[101–105] Testing continued to find synthetic belladonnoids with much shorter duration and with full recovery occurring within 1 to 2 days, making a convenient agent against which to test antidotes.[106–111]

Several other glycolates that were lower in potency but shorter in duration than BZ received limited testing.[112–115] BZ has often been incorrectly described as far stronger than LSD, and the reported "hundreds of compounds more potent than BZ" do not exist.[116] After the BZ program ended, enhanced glycolate formulations for use as incapacitating agents were deemed dangerous to develop and, because of their perceived slow onset time during evaluations, unsuitable for military use.

TREATMENT STUDIES

The ability to reverse the incapacitating effects of belladonnoids (or drugs such as LSD and opioids) is of paramount importance, not only for the sake of the affected individual, but also in any operation that needs to preserve fighting strength. Given in doses above their ID_{50}, belladonnoids, although eminently treatable, can be swift in action; a large number of troops in a delirious state would pose a serious problem for commanders. Fortunately in the case of BZ, during the onset and peak periods of drug action, somnolence (or even coma) would keep individuals virtually immobile for up to 24 hours—probably much longer with high doses. This somnolent period would provide time to place victims in a safe environment and treat them with an anticholinesterase to prevent the emergence of irrational behavior.

For at least 24 hours, subjects incapacitated by BZ show little inclination, and are unable, to act aggressively. This placidity is a pharmacological phenomenon. Aggression in mouse-killing rats, for example, is inhibited completely by BZ-like drugs. These rats otherwise attack and kill mice placed in their cage without delay. BZ and other belladonnoid agents could legitimately be called "calmatives." Lack of in-depth understanding of the 2- to 3-day delay between onset of delirium and partial recovery, which is the only time when behavior may become active and impulsive (though rarely aggressive), may have led to the conclusion that BZ use would provoke mayhem.

Before the mid 1960s, standard pharmacological textbooks taught that no antidotes, including cholinesterase inhibitors, were able to reverse belladonnoid delirium.[117] However, in 1963, the antidotal effectiveness of physostigmine was rediscovered at Edgewood Arsenal[118] when Goodman located and translated an 1864 report by an Austrian ophthalmologist on the successful use of Calabar bean extract (the natural source of physostigmine).[117] The report recounted the story of two prisoners who drank a quantity of tincture of belladonna, thinking it was alcohol. The physician called to attend them learned they had consumed belladonna, noted their saucer-like pupils, and suspected drug-induced delirium.[119] The doctor next reasoned that, because a few drops of Calabar extract reversed enlarged pupils and the loss of near vision caused by the belladonna drops he used for eye examinations, Calabar might have similar antidotal effects in the brain. To the most affected prisoner he gave a small amount of the extract in a spoonful of sugar and gave only plain sugar water to the other. Soon, the first man returned to a lucid state, able to describe the theft of the belladonna solution, while the second man remained unchanged.

Toward the end of the 1940s, perhaps seeking an alternative to insulin coma, a small group of psychiatrists began to use atropine to produce coma in psychiatric patients.[99–101] The physicians who introduced this unusual form of pharmacotherapy, unlike the authors of human pharmacology chapters at the time, were evidently aware that physostigmine could bring atropinized patients back to conscious awareness. They reported routinely administering 4 mg of physostigmine by injection soon after inducing a short period of atropine coma.

This useful finding received little attention from mainstream clinicians. The growing preference for neostigmine as treatment for such disorders as surgical ileus and myasthenia gravis had made physostigmine increasingly obsolescent. Neostigmine was valued for its lack of central effects, but physostigmine easily enters the brain and in fact may have been avoided because of its potential central toxicity. Anticholinesterase compounds other than physostigmine were also studied at the Edgewood clinical facility to determine their effectiveness as a BZ antidote. Even lethal nerve agents were evaluated as antidotes for BZ,[120,121] but their clinical application is highly impractical and inappropriate. Physostigmine was determined to be the safest and most appropriate antidote for BZ intoxication.

Repeated injections of physostigmine in BZ-exposed individuals, usually 2 to 4 mg at hourly intervals, maintained coherent speech and the ability to carry out tasks; without the physostigmine the individuals would have been continuously delirious for the next 2 to 3 days. In both cases, NF test scores rose dramatically when physostigmine was administered, reverted to an incapacitated level when physostigmine was temporarily withheld, and responded again when treatment was reinstituted.

In 1967 Edgewood physicians had published the first double-blind controlled study demonstrating the effectiveness of physostigmine in reversing scopolamine delirium.[118] Later they reconfirmed

this finding in studies of atropine and of Ditran (Lakeside Laboratories, Milwaukee, Wis), a 2 to 1 mixture of two similar belladonnoid glycolates.[89] In the late 1950s and early 1960s, Ditran coma (like atropine coma, a decade earlier) enjoyed brief popularity as a treatment for depression.[122–124] In Edgewood studies between 1962 and 1967, physostigmine proved equally effective as an antidote to the follow-on glycolates described above. Similar findings were soon reported in civilian studies.[125–128]

Deliria produced by overdose with other drugs possessing anticholinergic side effects, such as diazepam, tricyclic antidepressants, and antihistamines, were also found to be treatable with physostigmine.[128–130] When given by the intravenous route, a dose of 30 μg/kg of physostigmine was sufficient to partially reverse the anticholinergic delirium produced by a variety of belladonnoids, although at least 45 μg/kg was the initial dose required to obtain good results.

Physostigmine has also been used and reported to be effective for morphine-induced respiratory depression; alcohol withdrawal; and the effects of heroin, ketamine, and fentanyl.[131] Its mode of action in these instances may be partially due to a direct arousal effect, rather than simple inhibition of cholinesterase. Case reports confirming its efficacy have come from the director of the Rocky Mountain Poison and Drug Center, near Denver, Colorado.[125] The use of physostigmine as an antidote was also favorably reviewed by the director of the Poison Control Center in Munich, Germany.[132] Although in undrugged patients 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, the only unusual side effects were transient fasciculations of the platysma (a thin superficial neck muscle) in one subject, and transient periods of nausea and vomiting in a few others.[96]

If excessive physostigmine is given in the absence of belladonnoid intoxication, adverse effects can easily be reversed by injecting 1 to 2 mg of atropine. Physostigmine, if administered intravenously, should be given gradually because a bolus effect 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. Back titration with atropine can usually avert or reverse disturbing anomalies of response.

When the diagnosis is in doubt, an intramuscular test dose of 1 to 2 mg of physostigmine, repeated after 20 minutes if necessary, is recommended. Once the diagnosis of delirium has been established by a definite clearing of the sensorium, improvement can be sustained by repeating the treatment at intervals of 1 to 4 hours. Changes in heart rate and intellectual performance can provide a guide to dosage. For example, if heart rate rises and confusion increases (quickly assessable by asking for serial subtraction of 7s from 100), supplemental doses can safely be given. Polish investigators studying the effects of high-dose atropine treatment of psychiatric patients reported giving as much as 15 mg of physostigmine in a single injection to terminate atropine coma.[133] They did not describe any adverse effects.

Maintenance treatment of delirium produced by BZ or other long-acting agents is best handled by the use of oral physostigmine, mixing it with fruit juice to mask its bitter taste. Dosage by the oral route is only two thirds as effective as by the parenteral route and should be adjusted accordingly. In a combat zone, the oral route may, in fact, be the only practical way to treat large numbers of casualties. Medical technicians can do the job under the supervision of a physician.

For reasons that are not fully understood, physostigmine is relatively ineffective if given during the onset phase of belladonnoid intoxication. The treatment team should therefore not be discouraged if early administration of physostigmine fails to bring about immediate, dramatic improvement. Unfortunately, use of the antagonist does not shorten the duration of the underlying intoxication. Also, if initial treatment is not maintained, final recovery may be slightly delayed.[96] Although physostigmine is probably not as highly regarded as it was during the 1970s and 1980s, it has predictable effects, and there are specific indications for its use. Test doses of 1 mg may safely be given, and minor improvement in mental status, or a decrease in tachycardia, can justify the safe use of larger titrated doses.

Whether or not physostigmine is available, supportive measures are important. It may be proper to evacuate and hospitalize patients with severe cases. Oral tetrahydroaminacridine in doses of 200 mg was also tested as an antagonist against BZ and proved to be moderately effective.[93] Its use as an anticholinesterase treatment of Alzheimer patients has since been approved by the US Food and Drug Administration. In an Edgewood pilot study, tetrahydroaminacridine caused temporary mild changes in hepatic function tests, and further testing was discontinued. Similar changes were noted in civilian patients but did not prevent its approved use.

SAFETY OF THE GLYCOLATES

As with most drugs, the per kilogram lethality of BZ (for example) is progressively less in larger species. This relationship provides an extrapolated LD_{50} of 3 to 5 mg/kg, which would suggest a very high therapeutic ratio (more than 200). Such a safety margin is probably too optimistic, however, and a ratio of 40 has been accepted as a conservative, but more likely, estimate. The latter figure was calculated by noting that preferential affinity for peripheral (such as cardiac) rather than central muscarinic receptors seems to predict the lethality of the various belladonnoids. Before the Edgewood studies, central toxicity was usually considered the cause of death from atropine-like drugs, but it is more likely that cardiotoxicity rather than central respiratory failure is the usual cause of death.

Goodman collected data from hundreds of reports of lethality and survival following high doses of atropine (most of them published in the 19th century) to estimate its LD_{50}.[134] Abood reports survival of at least one individual who ingested more than 1,000 mg of atropine.[98] Recovery took 7 days. This case alone suggests that the LD_{50} is much higher than the values given in textbooks. The LD_{50} values for the various other belladonnoids were calculated by extrapolating from Goodman's estimate from atropine, taking into account the other drugs' relative central potency.[96] The therapeutic ratio for BZ obtained by this method is approximately 40. For scopolamine and other belladonnoids with high relative central potency, the therapeutic index is probably at least 100.

In actual use, inhalation doses would be highly variable, depending to a degree on weather conditions and methods of dissemination. The Operations Research Branch at Edgewood Arsenal computed dose distribution from a point source, ignoring wind and other factors. Although difficult to apply with confidence to a real-life situation, their results showed that airborne concentration would taper rapidly from any single source, causing a gradient of dosage.

A 1964 feasibility study (Project Dork) involved 10 volunteers and a team of medical personnel at Dugway Proving Ground, Utah.[94] The subjects, standing on a flatbed trailer that moved to track the cloud, inhaled small particles of BZ disseminated from a point source. Breath samples from their modified masks were fed to spectrophotometric devices, monitored by technicians and the physician, who watched the men and gave them telephonic directions from an airtight booth mounted just behind them. Cumulative dose measurements in real time allowed the physician to terminate the exposure when the putative median incapacitating exposure was reached. At 1,000 yards, 50 pounds of BZ, floated downwind under ideal atmospheric conditions, was required to reach the desired dose.

The volunteers actually had to jog in place for most of 40 minutes to inhale the required dose. Considering that the arc subtended by the cloud of BZ was probably no more than a few degrees, it would presumably take thousands of kilograms of BZ to produce incapacitating concentrations throughout 360° at a distance of 1,000 yards. Under less than ideal weather conditions it would take much more. This study provides some idea of the limitations of point source dissemination of agents possessing potency similar to that of BZ. It also underlines the importance of accurate logistical calculations.

The operations analysis group at Edgewood developed idealized models for the dissemination of aerosolized BZ. Realistic projections, however, would require giving appropriate weights to all the geographic, terrain, and atmospheric conditions in a given tactical situation. Evasive action and protective measures taken by the target population would add further variance. Aiming at a lower target dose would be one way to minimize lethality while attaining the desired goal of disrupting a group's ability to function. Taking care of those who were completely nonfunctional would divert those who were unaffected. It would then be necessary to rely on partly incapacitated personnel whose dependability would be uncertain. A military commander, even if personally protected from the agent, would undoubtedly find it difficult to contend with such a complicated situation, even if the median dose absorbed by his troops were only a fraction of the ID_{50}.

Another theoretical possibility is the use of combinations. For example, a rapidly acting but short-lasting belladonnoid could be mixed with a longer-acting agent that would take effect later and last from 1 to 3 days (depending on the choice). A more problematic but possibly effective mixture would be a fast-acting, potent opioid combined with a slower-acting belladonnoid. Opium was used to manage the agitation of belladonna delirium for centuries before physostigmine replaced it. Whether such a mixture would increase the danger of lethal overdose more than either agent used singly could only be learned from dose-response animal studies using various combinations of candidate opioids and belladonnoids.

DIAGNOSIS OF INCAPACITATING AGENT SYNDROMES

There seems little likelihood that agents other than anticholinergics, still the only drugs known to be effective and reasonably safe, would be useful on the battlefield. Several reports suggest that BZ-like agents have already been used, in Croatia and possibly elsewhere. It is improbable, however, that such agents would be used by nations (or groups such as Al Qaeda) whose predominant goal is the destruction of life. Nevertheless, elusive maladies are invariably reported after any major conflict. The probable overestimation of the number of injuries from Agent Orange exposure in the Vietnam War and the so-called "Gulf War syndrome" are 20th century examples of this phenomenon.[135] Medical officers must therefore be able to distinguish chemical intoxication from illnesses of nonchemical origin.

Impaired performance on the battlefield is much more likely to result from stress, illicit drug use, lack of motivation, or psychiatric illness than from a chemical agent. Intoxication produced by belladonnoid agents, by contrast, should be easy to recognize if the physician maintains the proper index of suspicion. Medical students were long taught the medical adage "dry as a bone, red as a beet, hot as a hare, and mad as a hatter" as a means of remembering the features of belladonna poisoning.

As discussed, glycolate anticholinergics can vary tremendously in their potency and duration of action. Signs and symptoms may last as few as 2 hours or as long as several weeks. Differential diagnosis may be more difficult with glycolates that produce few or no peripheral antimuscarinic features, especially at the low end of the incapacitating dose range. Even the pupils may not be greatly enlarged. Familiarity with the behaviors typical of delirium, 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 diagnosis in such cases.

Limited or covert use of other agents (those not suitable for large-scale dissemination) makes it important to recognize the effects of LSD and other psychedelics. Because 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. Laughter may supervene, but so may insubordinate and oppositional behavior. There are no practical diagnostic tests for psychedelic drugs (although a sensitive fluorometric method for quantitative detection of LSD is known, and refrigerated blood samples could be useful in making a definitive diagnosis at a later time).[44]

Marijuana intoxication is common in areas where the drug is indigenous, and the presence of reddened conjunctivae, along with the lack of concern and relaxed joviality that marijuana produces, should make the diagnosis obvious. There is little likelihood that purified tetrahydrocannabinols (the active component of cannabis) would be used in a general military setting. Blood and urine can be tested if definitive proof of cannabis use is needed, but such tests are not always feasible or available.

An important, sometimes overlooked cause of bizarre symptoms and behavior is anxiety, which can manifest as dizziness, tachycardia, sweating, headache, and even loss of sensation or ability to move parts of the body. Observation and reassurance may diminish these symptoms, providing a clue to the diagnosis. Comparable syndromes such as "soldier's heart," "Da Costa's syndrome," "shell shock," "combat neurosis," "combat fatigue," and "traumatic neurosis" are terms that arose during past wars to refer to incapacitation of psychiatric origin.[135]

Another important differential diagnosis is heat exhaustion, and more importantly, heat stroke. These conditions can also impair performance and may mimic glycolate intoxication. Individuals with heat stroke will not be sweating and may have warm, flushed, skin. They have very high temperatures (106°F or higher) and may be delirious, unconscious, or have seizures. Heat stroke is a medical emergency. These patients must have their body temperature reduced quickly and be monitored closely to prevent failure of critical organ systems.

Whether covertly or overtly delivered, the differential diagnosis of incapacitation is basically the same as used in typical emergency room overdose cases. Standard textbooks and manuals provide adequate guidelines, as in Table 12-1. The possibility that secret research might produce a highly potent, unfamiliar variant of a known psychoactive drug cannot, however, be ruled out. Blood or urine analysis would probably be needed to demonstrate the drug's presence and identify its chemical structure. Medical officers in the field would probably not have access to the instruments required for precise analysis, but their probability of facing completely unfamiliar chemical substances is low. Exhibit 12-1 is a summary of signs, symptoms, field detection, decontamination methods, and medical management of BZ and fentanyl derivatives.

TABLE 12-1

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
Sleepiness, ataxia, rapid unconsciousness, miosis, reduced quality of respirations decrease with resulting respiratory depression	Fentanyl (carfentanyl)

Data sources: (1) 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, MC1995: 3–1. Field Manual 8-285, NAVMED P-5041, AFJMan 44-149, FMFM 11-11. (2) US Army Medical Research Institute of Chemical Defense. *Medical Management of Chemical Casualties Handbook.* 4th ed. Aberdeen Proving Ground, Md: USAMRICD; 2007.

EXHIBIT 12-1

SUMMARY OF BZ AND FENTANYL DERIVATIVES

- **Signs and symptoms**
  - BZ and other glycolates: mydriasis; dry mouth; dry skin; increased deep tendon reflexes; decreased level of consciousness; confusion; disorientation; disturbances in perception and interpretation (illusions and/or hallucinations); denial of illness; short attention span; impaired memory.
  - Fentanyl derivatives (carfentanil): dizziness, sleepiness, ataxia, miosis (if there is no hypoxia; with hypoxia there is pupil dilation), rapid unconsciousness, vomiting, decreased respirations, central apnea, coma.
- **Field detection:** No field detector is available for either BZ or fentanyl derivatives.
- **Decontamination**
  - BZ: gentle but thorough flushing of skin and hair with water or soap and water is all that is required. Remove clothing.
  - Fentanyl derivatives (carfentanil): No decontamination required.
- **Management**
  - BZ
    - Antidote: physostigmine.
    - Supportive: monitoring of vital signs, especially core temperature.
  - Fentanyl derivatives (carfentanil)
    - Antidote: opioid antagonist naloxone/naltrexone.
    - Supportive: monitoring of vital signs. Proper positioning of patient to maintain airway is critical until effects of central respiratory depression diminish.

Adapted from: US Army Medical Research Institute of Chemical Defense. *Medical Management of Chemical Casualties Handbook.* 4th ed. Aberdeen Proving Ground, Md: USAMRICD; 2007.

EXHIBIT 12-2

ANCILLARY SUPPORTIVE MEASURES FOR THE TREATMENT OF DELIRIUM

- Control and containment are of primary concern because 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). Tethering or otherwise loosely restraining individuals who are disoriented is preferable to letting them move about freely without close supervision.
- 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.
- Dryness of the mouth and parching of the lips should be managed with moist swabs and small amounts of vaseline or unguents. Fluids should be given sparingly and food withheld until the individual is obviously capable of normal chewing and swallowing. If it is determined that the patient is cognizant enough to manage foods and has oral motor skills, hard candy may be given to induce sufficient salivation to keep the tongue moist.
- 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.
- Evacuation from the field to more adequate medical facilities is desirable in most cases. If evacuation is not possible, separation of the affected individuals into small groups (eg, in tents) is preferable to large aggregations, in which a few confused and hyperactive individuals can lead to an escalating problem of crowd control.

Adapted from: Ketchum JS, Sidell, FR. Incapacitating agents. In: Sidell FR, Takafuji ET, Franz DR, eds. *Medical Aspects of Biological Warfare.* In: Zajtchuk R, Bellamy RF, eds. *Textbook of Military Medicine.* Washington, DC: Department of the Army, Office of The Surgeon General, Borden Institute; 1997: 301.

MEDICAL MANAGEMENT

The standard measures for management of casualties apply to victims of incapacitating agents. Following provisional diagnosis, removal of the patient from the offending environment and decontamination are required. If aggressive agitation or delirium is present, segregation and even restraint measures may be needed, which should not be regarded as punitive (a volunteer who was grossly incompetent during an indoor simulation of a military outpost later commented that in battle he should be tied to a tree, since he would at least be protected from dangerous acts and would not remember it later anyway).

During the Korean conflict, Colonel Albert Glass and colleagues concluded that treatment close to the front lines produced a better psychiatric outcome than evacuation to medical facilities further to the rear. Heavy sedation was effective in dimming the memory of traumatic aspects of injury in patients whose primary problem was emotional. More often than not, a 3-day period of treatment with sedatives and supportive measures was sufficient to restore the fighting capacity of the affected soldier. This approach to treatment applies to incapacitating agents equally well when used with the appropriate antidotal regimen. Finally, as in any emergency, good training and common sense are the most important ingredients of good care. Exhibit 12-2 lists ancillary supportive measures for the treatment of casualties with delirium.

NONLETHAL WEAPONS: A POLICY PERSPECTIVE

This section discussed the policy context and history of the proposals to use or not to use the various potential "nonlethal," "low lethality," "reduced lethality," and "incapacitating agents."[2] The end of the Cold War modified the missions faced by the US military; direct involvement in asymmetrical conflicts became more important. Peacekeeping missions (in the Balkans); intervention in regional/civil conflicts (in the Balkans, the Caribbean, and Africa); and occupation in the face of an armed insurgency (in Afghanistan and Iraq) became common and drew US military forces into conflicts in which substantial civilian populations, often hostile, were involved. At the same time, intense satellite news coverage, often by foreign news media, meant that US military interactions with civilian crowds were under immediate and intense video scrutiny.

The taking of civilian hostages by terrorist groups has highlighted the need for interventions that would not cause casualties among hostages. This resulted in an increased military interest in NLWs to minimize unnecessary civilian casualties and property damage. Following the 1995 evacuation of United Nations forces from Somalia, where Marines were issued riot control agents (RCAs), the Marine Corps was given primary responsibility in July 1996 to develop new NLWs under the Joint Non-lethal Weapons Directorate.[25] This authority included evaluation of the legality and the usefulness of proposed new NLWs.

A number of chemical and biological weapons intended to be "incapacitating agents" of low lethality had been developed during the Cold War, but all have been banned by international treaties to which the United States is a party. The CWC bans development, production, and possession of any chemical weapon intended to cause death or "temporary incapacitation." The 1975 Biological Weapons Convention similarly bans biological or toxin agents with similar effects. The United States has renounced use of such weapons under any circumstances. These treaties prohibit not only the use but also the development or possession of these chemical and biological weapons.

RCAs, nonlethal chemical agents with effects that disappear spontaneously and quickly (within minutes) after exposure ceases, remain legal. The use of these agents, typically "irritant" chemicals (such as CN, CS, and OC) commonly referred to as tear gases, is constrained by the CWC. The CWC recognizes the legitimate use of RCAs by civilian police forces, or by military forces performing police-like duties, but prohibits use of RCAs "in warfare."

This prohibition had long been established by state parties to the 1925 Geneva Protocol, and the extensive use of RCAs in the Vietnam War by the United States to augment the effects of lethal weapons resulted in their specific inclusion in the CWC.[62] The United States does not consider RCAs to be chemical weapons, and US policy reserves the right to use RCAs under some limited military circumstances. However, US policy also recognizes that other nations (including some close allies) do not recognize these reservations as valid.[136] The United States has thus far opted not to employ RCAs in engagements in which organized armed combatants are active, such as the Iraqi insurgency.

Novel chemical or biochemical NLWs face substantial legal barriers to acceptance as legal weapons. Malodorants, if effective, presumably would qualify as RCAs, but as such their use in combat would be constrained. Useful chemical/pharmacological "calmatives" face substantially greater legal barriers. To be effective in military or paramilitary operations, their effects would likely need to be severe enough or persist long enough after exposure to qualify as causing "temporary incapacitation," so their development, stockpiling, and use would be banned by the CWC.

Even if such chemical agents were found to be acceptable under US interpretations of international law, de facto acceptability would depend on acceptance by the civilian political process and, as with the use of RCAs, would be influenced significantly by world opinion. Novel NLWs using new modalities such as acoustic, microwave, and laser effects are not currently constrained by treaty law; however, the immediate and long-term safety of such devices would doubtless be debated, possibly resulting in constraints (by unilateral US policy or by international treaty agreements) being applied after their introduction. The appearance of military lasers designed to permanently blind personnel in the 1990s resulted in the addition of a protocol to the 1980 United Nations Convention on Certain Conventional Weapons banning such devices. Although the United States has not yet ratified this protocol, it has agreed to abide by its terms.[137]

Considerable controversy over the desirability of developing and employing new NLWs exists.[22] Some US military opinion fears that employment of NLWs by military forces would be interpreted by adversaries as a lack of resolve to use lethal force.[138] Many in the international arms control community fear that development of biochemical NLWs would weaken or destroy existing treaty prohibitions against

chemical and biological weapons, and result in a renewed biochemical arms race involving both lethal and nonlethal agents that would not only increase the danger of chemical and biological warfare between national military organizations, but also allow proliferation of biochemical weapons technology to nonstate terrorist organizations.[139] Similarly, arms control advocates fear that development and employment of novel acoustic, microwave, and laser weapons would stimulate an arms race using these modalities, all of which lend themselves to easy modification into lethal or permanently disabling weapons.[86]

Other military and civilian opinion sees the development of modern NLWs as a method of reducing undesired and unintended collateral casualties when civilians are placed in danger during military or paramilitary operations. These advocates of new NLWs point out that restrictions or prohibitions on the use of new NLWs may result in the use of lethal weapons by default.[140] Perhaps the greatest uncertainty in NLW policy is how safe and effective new NLWs will be, and how the existing and future restrictions should be applied to their use against threats encountered in the changing circumstances of the 21st century.[140]

SUMMARY

The search for incapacitating agents capable of temporarily preventing military personnel from performing their duties (without permanent injury) has a long and colorful history. Candidate compounds offer promise, but, 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 NLW use by friendly nations has led to their elimination from the US arsenal. In the attempt to find an incapacitating agent that would meet the numerous constraints imposed by practical and political concerns, many studies were conducted, including the program at Edgewood Arsenal. Although an ideal incapacitating agent was never found, much was learned from the search.

A major medical benefit arising from the study of belladonnoids in volunteers was the demonstration that physostigmine (and other anticholinesterase agents) could be both effective and safe when properly used in healthy individuals. The usefulness of physostigmine has been recognized in mainstream medical practice; it has proven useful as an antidote for delirium brought on by belladonnoid overdose and other drugs with significant anticholinergic effects.

Reversible incapacitation by nonchemical methods or by psychedelic drugs such as LSD and other indole derivatives, as well as centrally active phenethylamines, tranquilizers, or antipsychotic drugs, are either insufficiently effective or carry risks that make their use unlikely. The recent use of potent opioids to release hostages from terrorists in Moscow resulted in high lethality, although Russia has considered the drugs safe enough for potential field use. More futuristic concepts, such as the use of agonists or antagonists at neuroregulator or neuromodulator receptor sites, do not appear to be feasible at the present time.

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