Chapter 30

DEFENSE AGAINST TOXIN WEAPONS

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SUMMARY

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INTRODUCTION

Toxins are biological agents that are produced by living organisms: bacteria, plants, or animals. Toxins differ significantly from replicating agents (viruses and bacteria) and from classic chemical agents. The physical characteristics and mechanisms of action of toxins, as a group, dictate how they must be used as weapons and how they may be defended against. The terminology used in the field of toxin weapons is specific, and the definitions given in Exhibit 30-1 will be used in this textbook.

Some of the toxins described in the chapters that follow have been identified by the intelligence community as biological warfare threats. The likely route of intoxication for soldiers or victims of terrorist attack is through the lung by respirable aerosols; another possibility is through the gastrointestinal tract by contamination of food or water supplies, although the latter would be difficult in chlorinated water; or in rivers, lakes, or reservoirs because of dilution effects. The effects of most toxins are more severe when inhaled than when consumed in food or injected by bites or stings. Other toxins can elicit a significantly different clinical picture when the route of exposure is changed, a phenomenon that may confound diagnosis and delay treatment. For the most part, physical measures, such as the protective mask and decontamination systems developed for the chemical threat, can protect against toxins.

UNDERSTANDING THE THREAT

Replicating agents (bacteria and viruses) are clearly accepted throughout the medical defense community to be biological agents—and there is no argument that classic chemicals are chemical agents. Toxins, however, have sometimes been claimed to be chemicals (saxitoxin and ricin are included in the chemical weapons convention as placeholders) and at other times to be biological agents. Even Article I of the 1972 Biological Weapons Convention contributes to this ambiguity by describing the agents in question as "Microbial or other biological agents, or toxins."[1]

The purpose of this chapter is to introduce toxins and describe their physical and biochemical characteristics, and the implications for medical defense, in the context of the clearly defined, and

EXHIBIT 30-1

TOXIN WEAPONS TERMINOLOGY

Toxin	Any toxic substance that can be produced by an animal, plant, or microbe. Some toxins can also be produced by molecular biological techniques (protein toxins) or by chemical synthesis (low-molecular-weight toxins). Chemical agents, such as soman, sarin, VX, cyanide, and mustard agents, typically man-made for weaponization, are not included in this discussion except for comparison.
Mass Casualty Biological (Toxin) Weapon (MCBW)	Any toxin weapon capable of causing death or disease on a large scale, such that the military or civilian infrastructure of the state or organization being attacked is overwhelmed. (NOTE: The commonly accepted term for this category of weapons is "weapons of mass destruction," although the term brings to mind destroyed cities, bomb craters, and great loss of life; MCBWs might cause loss of life only. I do not anticipate that "MCBW" will replace the term "weapons of mass destruction" in common usage, but it is technically more descriptive of toxin, and other biological, weapons.)
Militarily Significant (or Terrorist Weapon)	Any weapon capable of affecting—directly or indirectly, physically, or through psychological impact—the outcome of a military operation.

Source: Franz DR. *Defense Against Toxin Weapons*. Fort Detrick, Frederick, Md: US Army Medical Research Institute of Infectious Diseases; 1996: 4–5.

universally accepted, mass-casualty–producing agent classes. The following theoretical discussion is based on an understanding of physical and biochemical characteristics of toxins. It is not an intelligence assessment of the threat.

Toxins Compared With Chemical Warfare Agents

Toxins differ from classical chemical agents by source and physical characteristics. When considering them as biological warfare agents, the physical characteristics of the toxins are much more important than their source. Table 30-1 compares both types of agents. These are generalizations, and there are exceptions. The most important differences are in the areas of volatility and dermal activity. Toxins also differ from bacterial agents (eg, those causing anthrax or plague) and viral agents (eg, those causing viral equine encephalitides, or smallpox) in that toxins do not reproduce themselves.

Because toxins are not volatile, as are chemical agents, and with rare exceptions, do not directly affect the skin, an aggressor would have to present toxins to target populations in the form of respirable aerosols, which allow contact with the more vulnerable inner surfaces of the lung. This, fortunately, complicates an aggressor's task by limiting the number of toxins available for an arsenal. Aerosol particles between 0.5 and 5 μm in diameter are typically retained within the lung. Smaller particles can be inhaled, but most are exhaled. Particles larger than 5 to 15 μm lodge in the nasal passages or trachea and do not reach the lung. A large percentage of aerosol particles larger than 15 to 20 μm simply drop harmlessly to the ground. Because they are not volatile they are no longer a threat—even to unprotected troops. Although there are few data on aerosolized toxins, it is unlikely that secondary aerosol formation (ie, formation of 1–5 μm particles from larger, previously deposited droplets) caused by vehicular or troop movement over ground previously exposed to a toxin aerosol would generate a respirable toxin aerosol within the breathing zone of mounted or dismounted troops. (However, this may not be true with very heavy contamination with infectious agents such as anthrax spores, which might occur near the point of agent release from a munition.)

Toxicity, Ease of Production, and Stability

A toxin's toxicity, ease of production, and stability are inextricably interconnected. Regardless of its toxicity, a toxin that cannot be produced in sufficient quantity or is too unstable to survive as an aerosol after delivery cannot be an effective mass casualty biological weapon (MCBW). Slightly less toxic toxins that are easy and inexpensive to produce and deliver, and that are stable as aerosols, could be real threats, however.

TABLE 30-1

COMPARISON OF TOXINS AND CHEMICAL AGENTS

Characteristics	Toxins	Chemical Agents
Origin	Natural	Man-made
Production	Difficult, small-scale	Large-scale industrial
Volatility	**None volatile**	**Many volatile**
Relative Toxicity	Many are more toxic	Less toxic than many toxins
Dermal Activity	**Not dermally active***	**Dermally active**
Use	Legitimate medical use	No use other than as weapons
Odor and Taste	Odorless and tasteless	Noticeable odor or taste
Toxic Effects	Diverse toxic effects	Fewer types of effects
Immunogenicity	Many are effective immunogens†	Poor immunogens
Delivery	Aerosol delivery	Mist/droplet/aerosol delivery

*Exceptions are trichothecene mycotoxins, lyngbyatoxin, and some of the blue-green algal toxins. The latter two cause dermal injury to swimmers in contaminated waters, but are generally unavailable in large quantities and have low toxicity, respectively.
†The human body recognizes them as foreign material and makes protective antibodies against them.
Adapted from Franz DR. *Defense Against Toxin Weapons*. Fort Detrick, Frederick, Md: US Army Medical Research Institute of Infectious Diseases; 1996: 6.

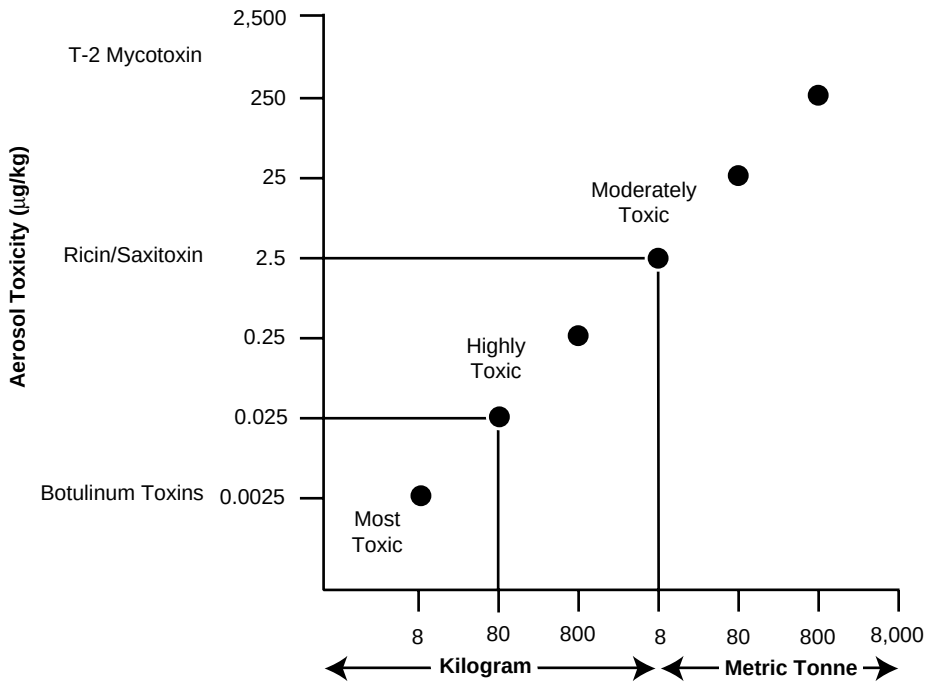

Fig. 30-1. Toxicity, in mouse LD_{50} (see Table 30-2), plotted against the quantity of toxin required to provide a theoretically effective open-air aerosol exposure, under ideal meteorological conditions, to an area of 100 km^2. Although the toxicity is based on direct studies with mice, it is believed to be very similar in humans. The mathematical model corrects for human parameters such as respiration. Ricin, saxitoxin, and botulinum, and trichothecene mycotoxins (T-2) kill at the concentrations depicted. Adapted from Spertzel RO, Wannemacher RW, Patrick WC, Linden CD, Franz DR. *Technical Ramifications of Inclusion of Toxins in the Chemical Weapons Convention (CWC)*. Alexandria, Va: Defense Nuclear Agency; 1992: 18. DNA Technical Report 92-116.

Because it must be delivered as a respirable aerosol, the utility of a toxin as an MCBW is limited by its toxicity and ease of production. The laws of physics dictate how much toxin of a given toxicity is needed to fill a given space with a small-particle aerosol. Figure 30-1 is a schematic representation of a theoretical calculation of the approximate quantities of toxins of varying toxicities required to intoxicate people exposed in large, open areas on the battlefield under optimal meteorological conditions. This figure is based on a mathematical model that was field tested in the 1960s (open-air testing) and found to be valid. It shows that a toxin with an aerosol toxicity of 0.025 mg/kg would require 80 kg of toxin to cover 100 km^2 with an effective cloud that exposes individuals within the cloud to a dose that would be lethal to approximately 50% of those exposed (LD_{50}). For example, a typical 70-kg soldier would have a 50% chance of surviving after receiving a 70-mg dose of a toxin with an LD_{50} of 1.0 mg/kg. Note that for toxins less toxic than botulinum or the staphylococcal enterotoxins, hundreds of kilograms or even tons would be needed to cover an area of 100 km^2 with an effective aerosol. Table 30-2 shows the mouse LD_{50}s of 25 toxins and chemical warfare agents.

During the U.S. biological warfare program, which ended in 1969, toxicity calculations were based on LD_{50} values as described above. The mathematical formulae developed by Calder and validated in field trials used the LD_{50} as a measure of toxicity.[2] Calculation of the LD_{50} of an aerosol requires a number of assumptions regarding respiratory minute volume of the experimental animal, and the percentage of the inhaled aerosol retained in the lung and airways during the period of exposure. In an attempt to improve accuracy, reproducibility, and data comparability within and between species, values called LCt_{50} values have been generated in recent years for aerosols. LCt_{50} is the product of the average concentration (C, in mg/m^3) and the exposure time (t, in min) that is lethal (L) to 50% of the population exposed (the units are expressed as $mg \cdot min/m^3$). LCt_{50} values for selected toxins in mice and rhesus monkeys are shown in Table 30-3.

TABLE 30-2

COMPARATIVE LETHALITY OF SELECTED TOXINS AND CHEMICAL AGENTS IN LABORATORY MICE

Agent	LD_{50} (μg/kg)*	Molecular Weight†	Source
Botulinum Toxin	0.001	150,000	Bacterium
Shiga Toxin	0.002	55,000	Bacterium
Tetanus Toxin	0.002	150,000	Bacterium
Abrin	0.04	65,000	Plant (rosary pea)
Diphtheria Toxin	0.10	62,000	Bacterium
Maitotoxin	0.10	3,400	Marine dinoflagellate
Palytoxin	0.15	2,700	Marine soft coral
Ciguatoxin	0.40	1,000	Fish, marine dinoflagellate
Textilotoxin	0.60	80,000	Elapid snake
Clostridium perfringens toxins	0.1–5.0	35,000–40,000	Bacterium
Batrachotoxin	2.0	539	Arrow-poison frog
Ricin	3.0	64,000	Plant (castor bean)
α-Conotoxin	5.0	1,500	Cone snail
Taipoxin	5.0	46,000	Elapid snake
Tetrodotoxin	8.0	319	Puffer fish
α-Tityustoxin	9.0	8,000	Scorpion
Saxitoxin	10.0 (Inhal: 2.0)	299	Marine dinoflagellate
VX	15.0	267	Chemical agent
Staphylococcus Enterotoxin B (Rhesus / Aerosol)	27.0	28,494	Bacterium
Anatoxin-A(s)	50.0	500	Blue-green algae
Microcystin	50.0	994	Blue-green algae
Soman (GD)	64.0	182	Chemical agent
Sarin (GB)	100.0	140	Chemical agent
Aconitine	100.0	647	Plant (monkshood)
T-2 Toxin	1,210.0	466	Fungal mycotoxin

*LD_{50}s are approximate, drawn from numerous published and unpublished sources. Routes of administration are typically intraperitoneal or intravenous.
†Note the general inverse relation between toxicity and molecular weight.
Reprinted from *Medical Management of Biological Casualties Handbook*. Fort Detrick, Frederick, Md: US Army Medical Research Institute of Infectious Diseases; Aug 1993: Appendix.

Ignoring other characteristics, if a toxin is not adequately toxic, sufficient quantities cannot be produced to make even one weapon. Because of their low toxicity, therefore, hundreds of toxins can be eliminated as ineffective as MCBWs. Certain plant toxins with marginal toxicity could be produced in large (ton) quantities. These toxins could possibly be weaponized. At the other extreme, several bacterial toxins are so lethal that MCBW quantities are measured not in tons, but in kilograms—

TABLE 30-3

LCt_{50}s FOR SELECTED TOXINS IN MICE AND RHESUS MONKEYS

Toxin	Mouse LCt_{50} ($mg \cdot min/m^3$)	Rhesus Monkey LCt_{50} ($mg \cdot min/m^3$)
Botulinum A	0.0225	0.0225
Ricin	3–7	114
Saxitoxin	3	—
T-2 Toxin	200	—
Staphylococcus Enterotoxin B	NA	80–100

Source: Pitt L, PhD. Chief, Department of Aerobiology and Product Evaluation, Toxinology Division, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Md. Personal communication, July 1996.

quantities more easily produced. Such toxins are potential threats to our soldiers on the battlefield.

Stability of toxins after aerosolization is also an important factor, because it further limits toxin weapon effectiveness. Some toxins are adequately toxic and can be produced in sufficient quantities for weapons, but are too unstable in the atmosphere to be candidates for weaponization. Although stabilization of naturally unstable toxins and enhanced production of those toxins now difficult to produce are possibilities for the future, no evidence exists at this time for successful amplification of toxicity of a naturally occurring toxin.

Incapacitation as well as lethality to humans must be considered. A few toxins cause illness at levels many times less than the concentration needed to kill. For example, toxins that directly affect the membranes, fluid balance, or both within the lung may greatly reduce gas transport without causing death. Less-potent toxins could also be significant threats as aerosols in a confined space such as a building; delivery could be into the filtration, heating, and air-conditioning systems. Finally, breakthroughs in delivery-vehicle efficiency or toxin "packaging" by an aggressor might alter the relation between toxicity and quantity; but even at best, the quantities needed could probably be reduced by only one half for a given toxicity. For now, however, the relation shown in Figure 30-1 provides a reasonable and valid way to sort potential threat toxins.

Militarily significant weapons need not be MCBWs. Thirty-nine Iraqi-modified Scud missiles reached Israel from 18 January through 28 February 1991. Although many of the Scuds were off target or malfunctioned, some of them landed in and around Tel Aviv. Approximately 1,000 people were treated as a result of the missile attacks, but only 2 died. Anxiety was listed as the reason for admitting 544 patients and atropine overdose for hospitalization of 230 patients.[3] The remainder (226 patients) suffered traumatic injury. Clearly, these Scuds were not effective mass casualty weapons, yet they caused significant disruption to the population of Tel Aviv. Approximately 75% of the 1,000 casualties were injured as a result of their own inappropriate actions or reactions. Had one of the warheads contained a toxin that killed or intoxicated a few people, the "terror effect" would have been even greater. Therefore, many toxins that are not sufficiently toxic for use in an *open-air MCBW* could probably be used to produce a *militarily significant weapon*. However, the likelihood that such a toxin weapon will cause panic among military personnel decreases when the leaders and troops become better educated regarding toxins.

Sources of Toxins and Their Mechanisms of Action

Toxins vary as to their source of production, molecular structure and size, and mechanism of action. Article I of the 1972 Biological Weapons Convention includes the concept of "toxins whatever their origin or method of production"[1] for good reason. Although in nature toxins are produced by microorganisms, plants, and animals, many of them can also be produced synthetically; this is generally not true of replicating agents. Ease of production—whether natural or synthetic—is obviously an important factor in evaluating a threat toxin, but a toxin's method of production does not change its molecular structure or mechanism of action.

Regarding molecular structure and size, the terms "low-molecular-weight" and "protein" toxins are commonly used. Low-molecular-weight toxins are typically less than 1,000 dalton (d), or approximately 10 amino acids, and may be either organic molecules or peptides. Protein toxins are proteins generally greater than approximately 10 amino acids.

The mechanism of action of a toxin does not necessarily correlate with either its source or its molecular structure or size. Understanding the mechanism of toxicity by the threat route of challenge is, however, the first step in developing medical countermeasures for a toxin, and is often the most important factor influencing what approach will be

taken to protect soldiers. For toxins, there are two general categories of mechanism of action:

1. Neurotoxins exert direct effects on nervous system function, most often the peripheral nervous system. These effects are typically temporary or reversible.
2. Membrane-damaging toxins actually destroy or damage tissues or organs, directly or indirectly through the release of mediators of disease. The effects of membrane-damaging toxins are less commonly reversible.

Although each of these factors will be discussed in detail in individual agent chapters, the concepts and their implications for the protection of soldiers are introduced here. There is little correlation between the artificial groupings (source, molecular structure, and mechanism of action) commonly used to categorize toxins. The natural source and the implications of mechanism of action of toxins on the development of medical countermeasures are discussed below.

Bacterial Toxins

The most toxic biological materials known are protein toxins produced by bacteria. They are generally more difficult to produce on a large scale than are the plant toxins, but they are many, many times more toxic. Botulinum toxins (seven related toxins), the staphylococcal enterotoxins (also seven different toxins), diphtheria, and tetanus toxin are well-known examples of bacterial toxins.

The botulinum toxins are so very toxic that lethal aerosol MCBW weapons could be produced with quantities of toxin that are relatively easily attainable with present technology. They cause death through paralysis of respiratory muscles without producing microscopic change in the tissues.

Staphylococcal enterotoxins, when inhaled, cause fever, headache, diarrhea, nausea, vomiting, muscle aches, shortness of breath, and a nonproductive cough within 2 to 12 hours after exposure. They can also kill, but only at much higher doses. Staphylococcal enterotoxin B (SEB) can incapacitate at levels at least 100-fold lower than the lethal level. These toxins, too, would probably be delivered as respirable aerosols.

Other bacterial toxins, classified generally as membrane-damaging, are derived from *Escherichia coli* (which produces hemolysins), *Aeromonas*, *Pseudomonas*, and *Staphylococcus*, (which also produce cytolysins and phospholipases), and are moderately easy to produce, but they vary a great deal in stability. Many of these toxins affect bodily functions or even kill by forming pores in cell membranes. In general, their lower toxicities make them less likely battlefield threats.

Marine Toxins

A number of the toxins produced by marine organisms, or by bacteria that live in marine organisms, might be used in terrorist biological weapons (where less agent would be needed to achieve the desired effect), but they are unlikely threats on the open battlefield. For many of these low-molecular-weight marine toxins, either difficulty of production or lack of sufficient toxicity limits the likelihood of their use as MCBWs.

Saxitoxin, the best known example of this group, is a potent neurotoxin found in shellfish such as mussels, clams, and scallops. Saxitoxin is a sodium channel–blocking agent and is more toxic by inhalation than by other routes of exposure. Unlike oral intoxication with saxitoxin (paralytic shellfish poisoning), which has a relatively slow onset, inhalational intoxication with saxitoxin can be lethal in a few minutes. Saxitoxin could be used against our troops as an antipersonnel weapon, but because it cannot currently be chemically synthesized efficiently, or produced easily in large quantities from natural sources, it is unlikely to be seen as an area aerosol weapon on the battlefield.

Tetrodotoxin, from the puffer fish and other members of the order Tetraodontiformes, is a neurotoxin much like saxitoxin in its mechanism of action, toxicity, and physical characteristics. Palytoxin, from the soft coral *Palythoa tuberculosa*, is extremely toxic and quite stable in impure form, but difficulty of production or harvest from nature reduces the likelihood that an aggressor would use it as an MCBW. The brevetoxins, commonly associated with "red tide" dinoflagellate blooms, and the blue-green algal toxins like microcystin, a hepatotoxin, have limited toxicity.

Fungal Toxins

The trichothecene mycotoxins, which are toxins produced by various species of fungi, are also examples of low-molecular-weight toxins (MW < 1,000 d). The yellow rain incidents in Southeast Asia in the early 1980s are believed to have demonstrated the utility of one of the trichothecene mycotoxins, T-2, as a biological warfare agent.

T-2 is one of the more stable toxins, retaining its bioactivity even when heated to high temperatures. High concentrations of sodium hydroxide and sodium hypochlorite are required to detoxify it. Aerosol toxicities are generally too low to make this class of toxins useful to an aggressor as an MCBW as defined in Figure 30-1; however, unlike most toxins, these are dermally active. Clinical presentation includes nausea, vomiting, weakness, low blood pressure, and burns in exposed areas.

Plant Toxins

Toxins derived from plants are generally very easy to produce in large quantities at minimal cost in a low-technology environment. Ricin, a protein derived from the bean of the castor plant, and abrin, a very similar toxin from *Abrus precatorius* are typical plant toxins.

Worldwide, approximately 1 million tons of castor beans are processed annually in the production of castor oil. The resulting waste mash is approximately 3% to 5% ricin by weight. Because of its marginal toxicity, at least 1 tonne (1,000 kg) of the toxin would be necessary to produce an MCBW (see Figure 30-1). Unfortunately, the precursor raw materials are available in these quantities throughout the world.

Venom Toxins

Animal venoms often contain a number of toxic and nontoxic proteins. Until recently, it would have been practically impossible to collect enough of these materials to develop them as biological weapons. However, many of the venom toxins have now been *sequenced* (ie, their molecular structure has been determined), and some have been cloned and *expressed* (ie, produced by molecular biological techniques). Some of the smaller ones could also be produced by relatively simple chemical synthesis methods. The following are examples of the mechanisms of action and sources of venom toxins:

- ion channel (cationic) toxins, such as those found in the venoms of the rattlesnake, scorpion, and cone snail;
- presynaptic phospholipase A_2 neurotoxins of the banded krait, Mojave rattlesnake, and Australian taipan snake;
- postsynaptic (curare-like alpha toxin) neurotoxins of the coral, mamba, cobra, and sea snakes, and the cone snail;
- membrane-damaging toxins of the Formosan cobra and rattlesnake; and
- coagulation/anticoagulation toxins of the Malayan pit viper and carpet viper.

Some of the toxins in this group must be considered potential future threats to our soldiers as large-scale production of peptides becomes more efficient. However, because many of these toxins are difficult to produce in large quantities, their threat potential may be limited.

Mechanisms of Action and the Development of Countermeasures

Unlike chemical agents, toxins differ widely in their mechanisms of action. The medical protection of soldiers is therefore difficult; seldom will a vaccine or therapy be effective against more than one toxin. (NOTE: We can prepare for a battlefield threat—unlike a terrorist threat—by developing specific medical countermeasures. Vaccines and other prophylactic measures can be given before combat, and therapies can be kept at the ready.) Countermeasures are discussed in general later in this chapter and in detail in specific agent chapters in this textbook.

Neurotoxins

Saxitoxin. Some neurotoxins, such as saxitoxin and tetrodotoxin, can kill an individual very quickly after inhalation of a lethal dose (within minutes). These toxins act by blocking nerve conduction directly and cause death by paralyzing muscles of respiration. Yet, at just less than a lethal dose, the exposed individual may not even feel ill, or may only feel dizzy.

Because of the rapid onset of signs after inhalation, prophylaxis (either immunization or pretreatment) would be required to protect soldiers from these two rapidly acting neurotoxins. Unprotected soldiers who inhale a lethal dose would probably die before they could be helped, unless they could be intubated and artificially ventilated immediately. Although the mechanism of death after inhalation of saxitoxin is believed to be the same as when the toxin is administered intravenously, it is more toxic if inhaled.

Botulinum Toxins. Other neurotoxins, such as the botulinum toxins, must enter nerve terminals before they can block the release of neurotransmitters, which normally cause muscle contraction. These large-protein neurotoxins generally kill by relatively slow onset respiratory failure (within hours to days). The intoxicated individual may not show

signs of disease for 24 to 72 hours. The toxin blocks biochemical action in the nerves that activate the muscles necessary for respiration, leading to suffocation.

Intoxications such as this can be treated with antitoxin injected hours after exposure to a lethal dose of toxin ($\leq$ 24 h in monkeys, and probably also in humans), and still prevent illness and death. Although the mechanisms of toxicity of the botulinum toxins appear to be the same after any route of exposure, the actual toxicity of the botulinum toxins is less by inhalation.

Membrane-Damaging Toxins

While neurotoxins effectively stop nerve and muscle function without causing microscopic damage to the tissues, membrane-damaging toxins destroy or damage tissue directly. For these toxins, prophylaxis is important, because the point at which the pathological change becomes irreversible often occurs within minutes to a few hours after exposure.

Microcystin. An example of this type of toxin is microcystin (produced by blue-green algae), which binds covalently to a phosphatase inside liver cells; this toxin does not damage other cells of the body. Unless uptake of the toxin by the liver is blocked, irreversible damage to the organ occurs within 15 to 60 minutes after exposure to a lethal dose. When this happens, the tissue damage to the liver is so severe that therapy may have little or no value. For microcystin, unlike most toxins, the toxicity is the same, no matter what the route of exposure.

Ricin. When dealing with membrane-damaging toxins, the consequences of intoxication, thus the pathogenesis of disease, may vary widely with route of exposure, even with the same toxin. Ricin, a plant toxin, kills by blocking protein synthesis in many cells of the body, but no lung damage occurs with any exposure route except inhalation. If ricin is inhaled, however, as would be expected during a biological attack, microscopic damage is limited primarily to the lung, and death is caused by a mechanism different from that of injected toxin. Furthermore, when equivalent doses of toxin are used, much more protective antibody must be injected to protect from inhalational exposure than from intravenous injection. Finally, although signs of intoxication may not be noted for 12 to 24 hours, microscopic damage to lung tissue begins within 8 to 12 hours or less. Irreversible biochemical changes may occur within 60 to 90 minutes after exposure, again making therapy difficult.

Trichothecene Mycotoxins. Only one class of easily produced, membrane-damaging toxins, the trichothecene mycotoxins, is dermally active. Therefore, they must be considered by standards different from those for all other toxins. Trichothecenes can cause skin lesions and systemic illness without being inhaled and absorbed through the respiratory system. Skin exposure and ingestion of contaminated food are the two likely routes of exposure of soldiers; oral intoxication is unlikely in modern, well-trained armies. Nanogram quantities per square centimeter of skin cause irritation, and microgram quantities cause necrosis. If the eye is exposed, microgram doses can cause irreversible injury to the cornea.

The aerosol toxicity of even the most toxic trichothecene is low enough that the large-quantity production required (approximately 80 tonnes to expose a 10-km^2 area with respirable aerosol) makes an inhalational threat unlikely on the battlefield. These toxins, therefore, might be dispersed as larger particles, probably visible in the air and on the ground and foliage.

In contrast to treatment for exposure to any of the other toxins, simply washing the skin with soap and water within 1 to 3 hours after exposure to the trichothecene mycotoxins will eliminate or greatly reduce the risk of illness or injury.

Populations at Risk

Because there are hundreds of toxins available in nature, the job of protecting troops against them seems overwhelming. It might seem that an aggressor would need only to discover the toxins against which we can protect our troops, and then pick a different one to weaponize. In reality, however, it is not that simple. The utility of toxins as MCBWs is limited by their toxicity (see Figure 30-1). This criterion alone reduces the list of potential open-air, weaponizable toxins for MCBWs from hundreds to fewer than 20. Issues related to stability and weaponization will not be addressed here, but would further reduce the list and make the aggressor's job more difficult.

An armored or infantry division in the field is not at great risk of exposure to a marine toxin whose toxicity is so low that 80 tonnes is needed to produce an MCBW covering 10 km^2. Most marine toxins are simply too difficult to produce in such quantities. Military leaders on today's battlefield should be concerned first about the most toxic bacterial toxins.

The more confined the military or terrorist target (eg, inside shelters, buildings, ships, or vehicles),

the greater the list of potential toxin threats that might be effective. This concern is countered, however, by the fact that toxins are not volatile like the chemical agents and are thus more easily removed from air-handling systems. It is probably most cost effective to protect our personnel from these less-toxic toxins through the use of collective filtration systems.

Nonetheless, we must consider subpopulations of troops and areas within which they operate when we estimate vulnerability to a given toxin threat. Because of differences in operational environments, situations could well occur in which different populations of troops require protection from different toxins. To protect them effectively, military decision makers and leaders must understand the nature of the threat and the physical and medical defense solutions.

Table 30-4 gives the approximate number of known toxins by toxicity level and source. To simplify our approach to the development of medical countermeasures, we have divided them into "Most Toxic," "Highly Toxic," and "Moderately Toxic" categories (also see Figure 30-1). The most toxic toxins could probably be used in an MCBW; it is feasible to develop individual medical countermeasures against them. The highly toxic toxins could probably be used in closed spaces such as the air-handling system of a building or as relatively ineffective terror weapons in the open; collective filtration would be effective against these toxin aerosols targeted to enclosed spaces. The moderately toxic toxins would likely be useful only as assassination weapons, which would require direct attack against an individual; it is not feasible to develop medical countermeasures against all of the toxins in this group. Such reasoning allows us to use limited resources most effectively and to maximize protection, and thus effectiveness, of our fighting force.

TABLE 30-4

ARBITRARY CATEGORIZATIONS* OF TOXIN TOXICITY

Source of Toxin	Most Toxic	Highly Toxic	Moderately Toxic	Total
	(Number of toxins in each category)			
Bacteria	17	12	> 20	> 49
Plants		5	> 31	> 36
Fungi			> 26	> 26
Marine organisms		> 46	> 65	> 111
Snakes		8	> 116	> 124
Algae		2	> 20	> 22
Insects			> 22	> 22
Amphibians			> 5	> 5
Total	**17**	**> 73**	**> 305**	**> 395**

*Most toxic (LD_{50} < 0.025 μg/kg), highly toxic (LD_{50} 0.025–2.5 μg/kg), moderately toxic (LD_{50} > 2.5 μg/kg)
Adapted from Spertzel RO, Wannemacher RW, Patrick WC, Linden CD, Franz DR. *Technical Ramifications of Inclusion of Toxins in the Chemical Weapons Convention (CWC).* Alexandria, Va: Defense Nuclear Agency; 1992: 13. DNA Technical Report 92-116.

COUNTERMEASURES

Physical Protection

As stated above, most toxins are neither volatile nor dermally active. Therefore, an aggressor would most likely attempt to present them as respirable aerosols. Toxin aerosols should pose neither a significant residual environmental threat nor remain on the skin or clothing. The typical toxin cloud would, depending on meteorological conditions, either drift with the wind close to the ground or rise above the surface of the Earth and be diluted in the atmosphere. There may, however, be residual contamination near the munition-release point. Humans in the path of a true aerosol cloud would be exposed as the agent drifts through that area. The principal way humans are exposed to such a cloud is through breathing. Aerosol particles must be drawn into the lungs and retained to cause harm.

The protective mask, worn properly, is effective against toxin aerosols. Its efficacy, however, depends on two factors: (1) mask-to-face or hood-to-head fit and (2) use during an attack. Proper fit is vital. Because of the extreme toxicity of some of the bacterial toxins, a relatively small leak could result in a significant exposure. Eyes should be protected when possible. Definitive studies have not been done to assess the effects of aerosolized toxins on the eyes. In general, however, ocular exposure to a toxin aerosol, unless the exposed individual is near the release point, would be expected to cause few systemic effects because of the low doses absorbed. A few toxins have direct effects on the eyes, but these are generally not toxins we would expect to be used as aerosols. Donning the protective mask prior to exposure would, of course, protect the eyes.

Because important threat biological warfare agents are not dermally active and must be pre-

sented as respirable aerosols, special protective clothing other than the mask is less important in a toxin attack than in a chemical attack. Presently available protective clothing should be effective against biological threats as we know them. Commanders should carefully consider the relative impact of thermal load and the minimal additional protection provided by protective clothing.

Real-Time Detection of an Attack

Because of the nature of the threat, soldiers may be dependent on a mechanical detection-and-warning system to notify them of impending or ongoing attack. Without timely warning, their most effective generic countermeasure, the protective mask, may be of limited value. Real-time detectors of a chemical agent attack have been successfully developed. Biological agent detectors will be more difficult to develop, for several reasons. As stated above, these agents must be presented as respirable aerosols, which act as a cloud, not as droplets (as the chemical agents are delivered) that fall to the ground and evaporate with time. The toxin cloud, typically delivered at night with a slight wind, would be expected to move across the battlefield until it either rises into the atmosphere to be diluted or settles, relatively harmlessly, to the ground. Unlike chemical agents, which might be detectable for hours, toxins might be detectable in the air *at one location only* for a few minutes. Definitive, specific toxin detectors would have to sample continuously or be turned on by a continuous sampler of some kind.

Furthermore, toxin detectors (assuming the present state of technology) would probably require the specificity of immunoassays to identify a toxin and differentiate it from other organic material in the air. Continuous monitoring by such equipment would be extremely costly, reagent-intensive, and very difficult to support logistically because of the reagent requirements. Identifying each toxin would require a different set of reagents if an immunoassay system were used.

Analytical assays would necessarily be more complex and less likely to identify distinct toxins, but they might detect that something unusual was present. Imagine the difficulty of developing a detection system based on molecular weight or other physical characteristics to differentiate among the seven botulinum toxins (molecular weight is the same for all, but each requires a different, specific antibody for identification or therapy).

Finally, to be effective, a detector would have to be located where it could "sniff" a toxin cloud in time to warn the appropriate population. This might be possible on a battlefield but would be nearly impossible, except in selected high-risk facilities, in the case of a terrorist attack. However, if all the capabilities described were developed and available at the right place and time, it is possible that an aerosol cloud of almost any of the toxins of concern could be detected and identified. Future advances in technology could well resolve our present technical difficulties.

Diagnosis: General Considerations

Medical personnel often ask whether they will be able to tell the difference among cases of inhalational botulinum, staphylococcal enterotoxin intoxication, and chemical nerve agent poisoning. Table 30-5 describes these differences. In general, nerve agent poisoning has a rapid onset (minutes) and induces increased body secretions (saliva, airways secretions), pin-point pupils, and convulsions or muscle spasms. Botulinum intoxication has a slow onset (12–72 h) and manifests as visual disturbance, skeletal muscle weakness and/or paralysis of oropharyngeal muscles. Staphylococcal enterotoxin B poisoning has an intermediate (few hours) time of onset and is typically not lethal but is severely incapacitating. Chemical nerve agent poisoning is a violent illness resulting in respiratory failure because of muscle spasm, airway constriction, and excessive fluid in the airways. Botulinum-intoxicated patients simply get very tired and very weak; if they die, it is because the muscles of respiration fail. Staphylococcal enterotoxin B–intoxicated patients become very sick but typically survive with supportive therapy.

Medical personnel should consider toxins in the differential diagnosis, especially when multiple patients present with similar clinical syndromes. Patients should be viewed epidemiologically and asked about where they were, whom they were with, what they observed, how many other soldiers were and are involved, and so forth. Inhaled and retained doses of toxins will differ among soldiers exposed to the same aerosol cloud. Those who received the highest dose typically will show signs and symptoms first. Others will present somewhat later, while still others in the same group may be unaffected. The distribution of severities within the group of soldiers may vary with type of exposure and type of toxin. For example, exposing a group of individuals to the staphylococcal enterotoxins by inhalation would likely make a large percentage (80%) of them sick, but would result in few deaths. Exposing a group

TABLE 30-5

DIFFERENTIAL DIAGNOSIS OF CHEMICAL NERVE AGENT, BOTULINUM TOXIN, AND STAPHYLOCOCCAL ENTEROTOXIN B INTOXICATION FOLLOWING INHALATIONAL EXPOSURE

Signs and Symptoms	Chemical Nerve Agent (Organophosphate)	Botulinum Toxin	Staphylococcal Enterotoxin B
Time to Onset	Minutes	Hours (12–72)	Hours (2–12)
Nervous	Convulsions, fasciculations	Progressive paralysis	Headache, muscle aches
Cardiovascular	Bradycardia	Normal rate	Normal rate or tachycardia
Respiratory	Difficult breathing, constricted airways	Normal, then progressive paralysis	Nonproductive cough In severe cases: chest pain, difficult breathing
Gastrointestinal	Increased motility, pain, diarrhea	Decreased motility	Nausea, vomiting and/or diarrhea
Ocular	Small pupils	Droopy eyelids	Conjunctival injection possible
Salivary	Profuse, watery saliva	Normal, but swallowing difficult	Slightly increased quantities of saliva possible
Death	Minutes	2–10 d	Unlikely
Response to Atropine/2-PAM Cl	Yes	No	Atropine may reduce gastrointestinal symptoms

2-PAM Cl: 2-pyridine aldoxime methyl chloride

of soldiers to a cloud of botulinum toxin might kill 50%, make 20% very sick, and leave 30% unaffected.

Medical personnel must consider the varying latent periods before onset of clinical signs. For patients exposed to toxins by aerosol, the latent period varies from minutes (saxitoxin, microcystin) to hours (the staphylococcal enterotoxins), even to days (ricin, the botulinum toxins).

Medical personnel must also save clinical and environmental samples for diagnosis. Immunoassays and analytical tests are available for many of the toxins. Environmental toxin samples taken directly from a weapon or other hardware are often easier to test than biological samples because they do not contain body proteins and other interfering materials.

The best early diagnostic sample for most toxins is a swab from the nasal mucosa. In general, the more-toxic toxins are more difficult to detect in tissues and body fluids, because so little toxin needs to be present in the body to exert its effect. The capability exists however, to identify most of the important toxins in biological fluids or tissues, and many other toxins in environmental samples. Definitive laboratory diagnosis might take 48 to 72 hours; however, prototype field assays that can identify some toxins within 30 minutes have been developed recently. For individuals who survive an attack with toxins of lower toxicity, immunoassays that detect immunoglobulins M or G offer a means of diagnosis, identification, or confirmation of agent within 2 to 3 weeks after exposure.

Approaches to Prevention and Treatment

In developing medical countermeasures, each toxin must be considered individually. Some incapacitate so quickly that there would be little time for therapy after an attack. Others cause few or no clinical signs for many hours, but they set off irreversible biochemical processes in minutes or a few hours that lead to severe debilitation or death several days later. Fortunately, some of the most potent bacterial protein toxins act slowly enough that, if they are identified, therapy initiated 12 to 24 hours after exposure is usually successful. Active and passive immunoprophylaxes are currently available but are not licensed for all high-threat toxins. Immuniza-

tion, pretreatment, and specific drug therapies are the subjects of considerable research interest.

Active Immunization

It is always better to prevent casualties than to treat injured soldiers. For most of the significant threat toxins in military situations, vaccination is the most effective means of preventing casualties. Unlike the chemical warfare agents, many of the important threat toxins are highly immunogenic. Immunized laboratory animals are totally protected from high-dose aerosols of these toxins. Immunization requires a knowledge of the threat, an available vaccine, and time. The minimum time needed to allow the body to make its own protective antibodies to a toxin may range from 4 to 6 weeks, to 12 to 15 weeks, or longer. Some vaccines currently in use require multiple injections, often administered weeks apart. The logistical burden of assuring that troops are given booster immunizations at the correct time could be overwhelming in a fast-moving buildup to hostilities.

The time and effort required for immunization can possibly be reduced. For example, antigens are being microencapsulated to form timed-release vaccines that might provide the primary immunization, a booster dose 2 weeks later, and another booster dose 10 weeks after that—all with one injection. Another approach is being evaluated with current Medical Biological Defense Research Program vaccines. Soldiers could be given a priming dose and the first booster dose 2 weeks apart, while in basic training. The response generated by the immune system's memory cells (ie, the B lymphocytes) might last for many months or even years, although not all soldiers would develop fully protective immunity after only two immunizations. Shortly before the onset of hostilities, or when the soldier is assigned to a rapidly deployable unit, one booster dose could provide protective immunity quickly, and preclude the need for additional booster doses after deployment. Preliminary data suggest that a booster dose administered up to 24 months (the greatest interval thus far tested) after two initial priming doses will be effective, even with moderately immunogenic vaccines such as the current botulinum toxoid.

Passive Antibody Prophylaxis

Passive antibody prophylaxis is generally quite effective in protecting laboratory animals from toxin exposure. However, this option is of little real utility for large groups of people for several reasons. The protection provided by human antibody may last for only 1 to 2 months, and protection afforded by despeciated horse antibody may last for only a few weeks. Therefore, antibody prophylaxis would be practical only when the threat is both clearly understood and imminent. Furthermore, it is unlikely that animal antibody would be used in an individual before intoxication because of the risk, albeit small, of an adverse reaction to foreign protein. The latter problem may be overcome within the next few years, as the production of human monoclonal antibodies or the "humanization" of mouse monoclonal antibodies becomes practical. Unfortunately, single monoclonal antibodies are seldom as effective against toxins as polyclonal antibodies, such as those produced naturally in other humans or horses. However, combined antibody therapy, or "cocktails" of more than one monoclonal antibody, may overcome this problem in the future.

Postexposure prophylaxis (ie, treatment after exposure but before signs and symptoms develop) with antibodies from human or animal sources is feasible for some of the threat toxins. Passive immunotherapy is very effective after exposure to botulinum toxin if treatment is begun soon enough, up to 24 hours after high-dose aerosol exposure to the toxin. The utility of antibody therapy drops sharply at or shortly after the onset of the first signs of disease. It appears that a significant amount of the toxin has, at that time, been taken up by areas of the body that cannot be reached by circulating antibodies. Antibody therapy given after the onset of signs may shorten the time that a patient must be given ventilatory support. The available antibody to botulinum toxin is produced in horses, and then despeciated to make a product with a reduced risk of adverse reaction that can be given to humans. Human monoclonal antibodies, or cocktails of two or more monoclonal antibodies, may be the next generation of antibody therapy. Passive antibody therapy such as that described here is more likely to be effective against neurotoxins like the botulinum toxins, which do not cause tissue damage, than against membrane-damaging toxins that induce mediator release (eg, staphylococcal enterotoxins), directly damage tissues (eg, ricin), or both.

Specific Therapy

Specific therapy with drugs presently has little value: most of the toxins either physically damage

cells and tissues very quickly (eg, ricin), or affect such basic mechanisms within the cell (eg, the neurotoxins) that drugs designed to reverse their effects are toxic themselves. Nevertheless, at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Frederick, Maryland, we have shown that rifampin stops the lethal intoxication by microcystin if it is given therapeutically to laboratory animals soon (15–30 min) after the toxin is administered.

Development of therapeutic drugs for toxins is presently aimed at several more general approaches. When the toxin's mechanism of action is understood and covalent (permanent) binding of the toxin to cellular protein does not occur (eg, ion-channel toxins), attempts are being made to discover drugs that compete with or block the toxin from binding to its site of action. For toxins with enzymatic activities, such as ricin and the botulinum toxins, drugs that serve as surrogate targets of such enzymatic action may be developed. For toxins such as botulinum, which block the release of a neural transmitter, there have been attempts to enhance the release of the needed transmitter by other means; the diamino pyridines are temporarily effective in reversing botulinum intoxication by this mechanism. Finally, for toxins like the staphylococcal enterotoxins and ricin, which induce the release of secondary mediators, specific mediator-blocking agents are being studied. In the future, drugs may well find a place in the therapy of some intoxications as adjuncts to vaccination or passive antibody therapy, or they may be used to delay onset of toxic effects.

Symptomatic Therapy

General supportive measures are likely to be effective in therapy of intoxication. Artificial ventilation could be lifesaving in the case of neurotoxins such as the botulinum toxins and saxitoxin. Oxygen therapy, with or without artificial ventilation, may be beneficial for intoxication with toxins such as ricin that directly damage the alveolar-capillary membrane of the lung. Vasoactive drugs and volume expanders could be used to treat the shocklike state that accompanies some intoxications (eg, with staphylococcal enterotoxin B). These measures could be used in conjunction with more specific therapies.

Decontamination and Protection of Medical Personnel

Recall that a true respirable aerosol will leave less residue on clothing and environmental objects than would the larger particles produced by a chemical munition. This suggests that decontamination would be relatively unimportant after a toxin aerosol attack. Because we lack field experience, however, prudence dictates that soldiers decontaminate themselves after an attack.

As a general rule, the decontamination procedure recommended for chemical warfare agents[4] effectively destroys toxins. Exposure to 0.1% sodium hypochlorite solution (household bleach) for 10 minutes destroys most protein toxins. The trichothecene mycotoxins require more stringent measures to inactivate them, but even they can be removed from the skin (although not inactivated) simply by washing with soap and water. Soap and water, or even just water, can be very effective in removing most toxins from skin, clothing, and equipment.

For the same reason that decontamination is only moderately important after individuals are exposed to a respirable toxin aerosol, medical personnel are probably at only limited risk from secondary aerosols. Because toxins are not volatile, casualties of a toxin attack can, for the most part, be handled safely and moved into closed spaces or buildings, unless they were very heavily exposed. Prudence dictates, however, that patients be handled as if they were chemical casualties or, at a minimum, that they be washed with soap and water. The risk to medical personnel is of greater concern with some agents. Secondary exposure might be a hazard with very potent bacterial protein toxins, such as botulinum toxin or the staphylococcal enterotoxins. (NOTE: Decontamination and isolation of patients or remains could be much more important and difficult after an attack with a bacteria or virus that replicates within the body.)

Remains of persons possibly contaminated with toxins should be handled the same as chemically contaminated remains. For the most part, toxins are more easily destroyed than chemical agents, and they are much more easily destroyed than anthrax spores. Chemical disinfection of remains in 0.2% sodium hypochlorite solution for 10 minutes would destroy all surface toxin (and even anthrax spores), greatly reducing the risk of secondary exposure.

Sample Collection: General Rules for Toxins

Identifying toxins or their metabolites (breakdown products) in biological samples (blood, urine, feces, saliva, or body tissues) is difficult for several reasons. First, for most toxic toxins, relatively few

molecules of toxin need be present in the body to cause an effect; therefore, finding them requires extremely sensitive assays. Second, the most toxic toxins, and those most likely to be seen on the battlefield, are proteins. Therefore, after they break down, these toxins and toxin fragments can be unidentifiable in the human body.

Third, we must generally look for the toxin itself or its metabolites, not an antibody response, as can be done with infectious agents. Anyone receiving a lethal dose of any of the toxins would be unlikely to live long enough to be able to mount an antibody response. However, with certain protein toxins (ricin and the staphylococcal enterotoxins) that are highly immunogenic and less lethal, we might see antibodies produced in soldiers who received a single exposure and survived. These might be seen as early as 2 weeks after exposure.

Certain toxins can be identified in the sera of animals, and therefore probably of humans, exposed by inhalation. Blood samples should be collected in sterile tubes and kept frozen, or at least cold, preferably after clotting and removal of cells. If collected within the first day, swab samples taken from the nasal mucosa are the best early diagnostic samples in which to identify several of the toxins. These too, should be kept cold. As a general rule, all samples that are allowed to remain at room temperature (approximately 75°F–80°F) or higher for any length of time will have little value.

Biological samples from patients are generally not as useful for diagnosis of intoxications as they are for diagnosis of infectious diseases or chemical intoxications. The same is true of postmortem samples. Ricin can be identified with immunoassays in extracts of lung, liver, stomach, and intestines up to 24 hours after aerosol exposure. High doses of ricin can be identified in fixed lung tissue of aerosol-exposed laboratory animals by immunohistochemical methods. The staphylococcal enterotoxins can be detected by immunoassay in bronchial washes. Like blood and swab samples, postmortem tissue or fluid samples should be kept cold, preferably frozen, until they can be assayed.

Environmental samples from munitions or swabs from environmental materials should be placed in sealed glass or Teflon (polytetrafluoroethylene, manufactured by Du Pont Polymers, Wilmington, Delaware) containers, and kept dry and as cold as possible. CAUTION: Handling a dry or powdered toxin can be very dangerous because the toxin may adhere to skin and clothing and could be inhaled.

Toxin Analysis and Identification

Immunological or analytical assays or both are available for most of the toxins discussed in this chapter. Immunological methods, typically enzyme-linked immunosorbent assays (ELISAs) or receptor-binding assays, are sensitive to 1 to 10 ng/mL and require approximately 4 hours to complete; these are being developed as the definitive diagnostic tests for deployed units. Analytical (chemical) methods are sensitive at low-microgram to high-nanogram amounts, and take approximately 2 hours to run plus time for instrument setup and isolation or matrix removal (ie, removal of normal body proteins and other contaminating material) when necessary; the latter can add days to the process. A small, sensitive, far-forward, fieldable assay for several toxins has been developed, and similar kit assays are being developed for many of the other toxins described in this chapter. The polymerase chain reaction (PCR) technique, which provides very sensitive means of detecting and identifying the genetic material of any living organism, can be used to detect remnants of the bacterial, plant, or animal cells that might remain in the crude, impure toxin that we would expect to find in a weapon. Finally, a new method of combining immunoassays with PCR may allow us to detect extremely small quantities of the toxins themselves. In their present state, PCR assays are best suited for use in the reference laboratory.

Water Treatment

Questions often arise regarding the protection of water supplies from toxins. It is unlikely that a small-particle aerosol attack with toxins of military concern would significantly contaminate water supplies. Furthermore, as a general rule, direct contamination of water supplies by pouring toxins into the water would need to be done downstream of the processing plant and near the end user, even for the most toxic bacterial toxins—and ordinary chlorination methods are effective against some of the most potent toxins. Because of dilution, adding toxins to a lake or reservoir would be unlikely to cause human illness. Natural production of algal toxins (eg, microcystin) in stagnant bodies of water could produce enough toxin to cause illness if that water were used for drinking. Three methods of water purification have been tested for the threat toxins (Table 30-6).[5]

TABLE 30-6

WATER PURIFICATION METHODS EFFECTIVE AGAINST TOXINS

Method	Toxin (MW in d)	Effectiveness
Reverse Osmosis	Ricin (64,000)	Effective
	Microcystin (1,000)	Effective
	T-2 mycotoxin (466)	Effective
	Saxitoxin (294)	Effective
	Botulinum toxins (150,000)	—*
	Staphylococcal Enterotoxin B (28,494)	—*
Coagulation/Flocculation	Ricin	Not effective
	Microcystin	Not effective
	T-2 mycotoxin	Not effective
	Saxitoxin	Not effective
	Botulinum toxins	—†
	Staphylococcal Enterotoxin B	—†
Free Chlorine (household bleach)	Ricin	Not effective
5 mg/L (5 ppm) for 30 min	Microcystin	Not effective
	T-2 mycotoxin	Not effective
	Saxitoxin	Not effective
	Botulinum toxins	Destroys the toxins
	Staphylococcal Enterotoxin B	—†

*Not tested but expected to be effective
†Not tested but *not* expected to be effective
Data source: Wannemacher RW Jr, Dinterman RE, Thompson WL, Schimdt MO, Burrows WD. *Treatment for Removal of Biotoxins From Drinking Water*. Fort Detrick, Frederick, Md: US Army Biomedical Research and Development Laboratory; Sept 1993. Technical Report 9120.

THE FUTURE

Toxins as Weapons

Research literature suggests that the majority of the "most toxic" ($LD_{50} < 0.025$ μg/kg) naturally occurring toxins have already been discovered. New toxins of lesser toxicity, especially the venom toxins, are being discovered at the rate of perhaps 10 to 20 per year. There is little precedence in the literature for artificially increasing the toxicities of naturally occurring toxins; however, it might be possible to increase the physical stability of toxins that are toxic enough but too unstable to weaponize. This could increase the effectiveness of a toxin that is currently considered to be a low threat.

It is unlikely that chemical synthesis of complex nonprotein toxins will become significantly easier in the near future. It is likely, however, that large-scale biosynthesis of peptide toxins of 10 to 15 amino acids (some of the venom toxins) will become possible in the next few years.

Countermeasures to Toxins

Although the threat of toxin weapons of the future is formidable, the prospect of new and better medical countermeasures is brighter than ever before. Biotechnology may have more value to those of us who are developing countermeasures than to those who would use toxins maliciously. Molecular biological techniques that have been developed in the last few years now allow us to produce more-effective and less-expensive vaccines against the protein and peptide toxins. Such vaccines will likely

be available for the most important toxins within the next few years.

We are making good progress on developing recombinant vaccines for certain high-threat toxins. In the future, protection of our soldiers from toxin threats will be limited only by our willingness to use the vaccines. Similar technology allows us to produce human antibodies, which will eventually replace those now produced in animals. Human antibodies will be a significant advance over despeciated horse antibodies, possibly allowing us to protect unvaccinated soldiers by simply giving them an injection before they go into battle, thereby providing immediate protection. Human antibodies could also be used therapeutically in treating victims of a terrorist attack.

SUMMARY

Protecting soldiers on the battlefield from toxins—and replicating agents—is possible if we use our combined resources effectively. Physical countermeasures such as the protective mask, protective clothing, and decontamination capabilities exist and are effective. As we improve our battlefield detection systems, early warning of our soldiers may become a reality, at least in subpopulations within our forces. These assets, unlike most medical countermeasures, are generally generic and protect against most or all of the agents.

Among the medical countermeasures, vaccines are available and effective for some of the most important agents, and therapies exist for others. Because of limited resources available to develop vaccines, diagnostic methodologies, and therapies, we can field specific medical countermeasures only to a relatively small group of threat agents. Our efforts in this area must be carefully focused.

A third and complementary element of our defensive program must be good intelligence. Only through knowledge of specific threat agents, delivery systems, and national capabilities can we assure the effective development and use of our physical and medical countermeasures.

Finally, our renewed understanding of the real strengths and weaknesses of toxins as weapons allows us to put them in perspective in educating our soldiers, removing much of the mystique—and associated fear—surrounding toxins. Knowledge of the threat thus reduces the threat to our soldiers.

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