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TEACHERS' TOPICS

Pharmacotoxicology of Chemical and Biological Terrorism

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Terrorism is the threat or implementation of violent means to undermine, destabilize, inflict harm, or cause panic in a society. The public's awareness of a variety of potential resources that could be used in terrorist threats has prompted unprecedented societal responses. Terrorist methods include the use of radiological, chemical, and biological agents capable of widespread mass casualties and destruction. The ease of availability, the low cost of production, and the potential for widespread dissemination of these means of destruction make them very attractive weapons. For these reasons, a basic understanding of pharmacotoxicology should be an essential part of the pharmacy school curriculum.
Keywords: Bioterrorism, pharmacotoxicology, biological toxins, chemical toxins, instructional methods

INTRODUCTION

In the *Pharmacotoxicology* course (PHS 4404) at the College of Pharmacy at St. John's University, each lecture begins with a summary of the basic principles necessary to understand the course material. Overall, the course emphasizes the clinical consequences of exposure to pharmacological agents. Other areas of discussion include clinical toxicology of nontherapeutic chemicals, such as gases and metals.

The objective of the *Pharmacotoxicology* course is to present current topics in clinical toxicology as they apply and relate to societal concerns, with an emphasis on the role of chemical and biological toxicity in the health care field. The series of lectures presented emphasizes the history, routes, signs and symptoms, and pathophysiology of chemical exposure. Treatment and prevention of toxicity and disease is mentioned. Extensive protocols of pharmacologic intervention and emergency preparedness are not presented since those topics are within the scope of emergency medicine rather than pharmacotoxicology.[1]

Lectures used for this article follow a series of working guidelines created by the Emergency Preparedness and Response initiative of the Centers for Disease Control and Prevention to help prepare against the threat of bioterrorism.[2] A summary of high-priority chemical and biological agents is compiled in Table 1 and ranked according to their potential use as bioterrorist threats.

Category A includes high-priority agents and pathogens rarely seen in the United States that pose a risk to national security. They are highly infectious, easy to disseminate, and the clinical effects from exposure result in high mortality rates. Category A agents are capable of inciting public panic and disruption, thus requiring special public health preparedness. Category B lists the second-highest priority agents. These organisms are moderately easy to disseminate, result in moderate morbidity and low mortality rates, and the threat of their use requires specific enhancements of the CDC's diagnostic capacity and enhanced disease surveillance. Category C includes pathogens that could be engineered for mass dissemination. Emerging threats, such as the Nipah virus and hantavirus, are available and easily produced and disseminated provided there exists some technical knowledge of microbiology. Thus, they have the potential for causing high morbidity and mortality.

The following lecture from the course is on chemical and biological terrorism and is prefaced by a review of bacterial and viral physiology, since most of the biological threats to public safety are of bacterial or viral origin (although most senior undergraduate toxicology students have studied fundamental biology and physiology, they appreciate the informative "refresher." Some of the biological and chemical agents discussed in this lecture that pose a risk to national security appear in Table 1. The lecture material encompasses two 2-hour sessions for senior toxicology majors, and it is one of the last topics in the 4-credit course. The toxicology of other chemicals not presented here but included in previous lectures are summarized in Table 2.

Chemical toxicity, due to agents such as nerve gases, is discussed in previous lectures and outlined in this lecture within the context of chemical applications of terrorism. Consequently, this lecture elaborates primarily on

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Table 1. Chemical and Biological Agents with Risk to National Security

Category	Category Description	Toxin or Disease	Causative Agent	Classification
A	Highly infectious, easily disseminated, high mortality rate	Anthrax	*Bacillus anthracis*	Spore-forming bacteria
		Botulism	*Clostridium botulinum*	Spore-forming bacteria
		Plague	*Yersinia pestis*	Enterobacteria
		Smallpox	Variola, vaccinia*	Poxvirus
		Tularemia	*Francisella tularensis*	Coccobacillus
		Hemorrhagic fever	Lassa, Junin, Machupo	Arenavirus
B	Moderate rates of infection, dissemination, morbidity and mortality	Brucellosis	*Brucella sp.*	Coccobacillus
		Epsilon toxin	*Clostridium perfringens*	Spore-forming bacteria
		Acute gastroenteritis	*Salmonella sp., Shigella sp., E. coli*	Enterobacteria
		Q fever	*Coxiella burnetii*	Obligate intracellular bacillus
		Ricin toxin	*Ricinus communis*	Castor beans
C	Highly infectious, ease of dissemination unknown	Hemorrhagic fever	Hantavirus	Bunyaviridae
		Encephalitis	Bunyavirus	
		Encephalitis	Nipah virus	Paramyxoviridae

* Variola is the extinct human virus; vaccinia is the laboratory product used for smallpox vaccinations.

the mechanisms of pathogenic agents and their toxic biological products, some of which only recently have been identified as potential toxic terrorist threats (Table 1).

BIOLOGICAL PATHOGENS AND TOXINS AS THREATS TO PUBLIC SAFETY

Naturally occurring or laboratory-derived biological pathogens and their products, released intentionally or accidentally, can result in disease or death. Human exposure to these agents may occur through inhalation, skin (cutaneous) exposure, or through ingestion of contaminated food or water. Following exposure, physical symptoms may be delayed and sometimes confused with naturally occurring illnesses, thus contributing to possible postponement in the emergency response to this threat. In addition, biological warfare agents may persist in the environment and cause problems long after their release.

The organisms presented here fall into 3 major classes of microorganisms: bacteria, rickettsia, and viruses. In addition, hazardous bacterial toxins are produced as byproducts of their pathogenic metabolism. Brief descriptions of some of the high-priority infectious agents and their products are outlined below; pathology and treatments are also noted where appropriate.[3-8]

Anthrax (*Bacillus anthracis*)

Anthrax is an infectious disease caused by the spore-forming bacterium, *Bacillus anthracis*. Depending on the source, the organism is either an obligate or facultative aerobe. The highly resistant, prominent polypeptide capsule of the endospore renders *B. anthracis* immune to most methods of disinfection or natural processes of inactivation. Thus, the organism may be present in soil for decades, occasionally infecting grazing goats, sheep, or cattle. When ingested, the hibernating, dehydrated, protected spores release viable bacteria upon contact with gastrointestinal fluids. Human infection occurs by 3 routes of exposure to anthrax spores: cutaneous, gastrointestinal, and inhalation. Although human cases of anthrax are infrequent in North America, the United States military views anthrax as a potential biological terrorist threat because of its high resistance and ease of communicability through the air.

Cutaneous infection is the most common manifestation of anthrax in humans, accounting for 95% of cases. Inoculation through exposed skin results from contact with contaminated soil or contaminated animal products such as hair, hides, and wool. A painless papule at the site of inoculation progresses rapidly to an ulcer surrounded by vesicles, and then to a necrotic eschar. Systemic infection, complicated by massive edema and painful lymphadenopathy, is fatal in 20% of patients.

Ingestion of undercooked or raw meat infected with the bacterium causes the rare gastrointestinal infection. This is characterized by an acute inflammation of the intestinal tract. Initial signs of nausea, anorexia, vomiting, and fever are followed by abdominal pain, bloody vomitus, and severe diarrhea. As with the cutaneous form, systemic disease can progress rapidly.

Respiration of dried, airborne spores leads to inhalation anthrax (eg, "wool-sorters' disease"). Initial symptoms of inhalation anthrax follow a prolonged, asymptomatic latent period (1 week to 2 months), and include

Table 2. Summary of Chemical Agents Previously Discussed in Class with Potential for Use as Bioterrorist Weapons

Chemical	Industrial* or Household Uses	Chemical Properties	Acute Effects
Acrylonitrile	Acrylics, fumigant, chemical intermediate	WS, LS, F, explosive	Cyanide toxicity, skin vesiculation, dermatitis
Arsine (AsH_3)	Glass, enamels, herbicides, textiles, preservative	Neutral gas, slightly WS (*garlic odor*)	Local irritation, hemolysis, renal failure, peripheral neuropathy
Benzyl bromide	Chemical war gas	Liquid, decomposed by water	Intense local irritation; large doses causes CNS depression
Carbon disulfide	Electroplating, degreaser, production of rayon	F liquid	Peripheral neuropathy, euphoria, restlessness, N, V
Carbon monoxide	Product of industrial combustion	Odorless, colorless, nonirritating gas	Asphyxiant
Cyanide	Electroplating, fumigants, fertilizers	Various salts, gas (HCN)	Effects due to histotoxic anoxia
Hydrogen	Welding, chemical production, thermonuclear reactors	Colorless, odorless flammable, explosive gas	Asphyxiant
Methane	Illuminating & cooking gas, organic synthesis	Colorless, odorless flammable gas, lighter than air	Asphyxiant
Ozone	Disinfectant, bleaching, oxidizing agent	Bluish explosive gas or liquid, oxidizing agent	Irritation, pulmonary edema, chronic respiratory disease
Phosgene	Production of solvents, plastics, pesticides	Colorless gas, poor WS	Pulmonary edema, URT irritation
TEPP	Organophosphorous insecticide	Liquid, agreeable odor, WS, LS	Exaggerated cholinergic muscarinic stimulation

*Used in manufacturing, synthesis, or as part of industrial processes.
Abbreviations: CNS = central nervous system, F = flammable, LS = lipid soluble, N = nausea, URT = upper respiratory tract, V = vomiting, WS = water soluble

fever, dyspnea, cough, headache, vomiting, chills, and chest and abdominal pain. A progressive, dramatic worsening of the infection occurs after several days, characterized by fever, pulmonary edema, and lymphadenopathy. Shock and death occur within 3 to 7 days after initial signs and symptoms occur.

The mortality rates from anthrax vary, depending on exposure and age, and have been adjusted according to the recent experience with the United States postal anthrax threats in the fall of 2001. A mortality rate of approximately 20% is seen with cutaneous anthrax without antibiotics, and a rate of 25% to 75% is seen for gastrointestinal anthrax. With aggressive treatment, the fatality rate for inhalation anthrax is about 50%. Anthrax is susceptible to early antibiotic treatment with penicillin, doxycycline, and fluoroquinolones. The anthrax vaccine is also an effective control measure and is in use in the United States armed forces; it is not available to the general public, however, and is not recommended to prevent disease.[9]

Botulism

Botulism is caused by *Clostridium botulinum*, a gram-positive, spore-forming anaerobic rod. Like *B. anthracis*, the bacterium lives in soil and in the intestines of animals. Besides botulism, production of protein toxins by the variety of clostridial species is associated with a range of diseases, including tetanus, gas gangrene, food poisoning, diarrhea, and pseudomembranous colitis.

Botulism is caused by the release of preformed botulinum toxin secreted by the organism in contaminated food. Interestingly, the organism's presence in the food or its existence in the victim's gastrointestinal tract is not necessary for virulence. Anaerobic conditions favor the growth of the spores in contaminated meats, vegetables and fish. The heat-resistant spores survive food processing and canning in sufficient numbers to cause toxicity upon release of the toxin.

The botulinum toxin is a neurotoxin capable of preventing the release of acetylcholine at peripheral cholinergic synapses. Clinically, the disease has an onset of 12 to 36 hours. Signs and symptoms are related to inhibition of skeletal muscle innervation and include: flaccid muscular paralysis, blurred vision, difficulty swallowing, and respiratory paralysis. Striated muscle groups weaken because of the descending paralysis, eventually affecting the neck and extremities.

Supportive care and maintenance of vital functions, especially respiration, is of utmost importance in treatment. Specific antitoxin is available for some of the neu-

rotoxin types (A, B, and E). With good supportive care and antitoxin administration, the mortality rate is reduced to 25%. Muscle paralysis may be prolonged or permanent.

Plague (*Yersinia pestis*)

Plague is an infectious disease of animals and humans caused by the bacterium *Yersinia pestis*.[10] All yersinia infections are zoonotic, capable of spreading from rodents and their fleas (urban plague), as well as from squirrels, rabbits, field rats, and cats (*sylvatic plague*). Historically, pandemics resulting from *Yersinia* infections have devastated human populations. The middle ages (1320s) recorded a pandemic that probably originated from Asia and spread through Europe, resulting in 25 million deaths in Europe. Recent history (1895) recorded a pandemic that began in Hong Kong and spread to Africa, India, Europe, and the Americas, leaving 10 million deaths in its wake over 20 years. The recognition of public health and maintenance of hygienic standards has essentially eradicated urban plague from most communities, although some cases are reported annually in the United States. Clinically, *Y. pestis* infections are manifested as bubonic plague and pneumonic plague.

The bite of an infected flea starts the incubation period for *Y. pestis* of about 7 days. The resulting clinical signs and symptoms of bubonic plague include the development of buboes (swelling of the axillary or inguinal lymph nodes) and fever. In the absence of antibiotics, fatal bacteremia rapidly develops.

Aerosolized transmission of *Y. pestis* characterizes the highly infectious pneumonic plague. Person-to-person transmission occurs through close inhalation of infected respiratory droplets. A shorter incubation period results in fever, headache, malaise, and a cough accompanied by blood and mucus. Without early antibiotic intervention, the pneumonia progresses rapidly over 2 to 4 days to septic shock and death.

Early treatment with streptomycin, tetracycline, and chloramphenicol is effective in treating pneumonic plague. Prophylactic antibiotic treatment for 7 days will protect persons at risk for close contact with infected patients. There is no vaccine against plague.

Brucellosis (*Brucella suis*)

Brucellosis is caused by the gram-negative coccobacillus bacteria of the genus *Brucella*. Infections are generally zoonotic, with animal reservoirs maintained in sheep, goats, cattle, deer, elk, pigs, and dogs. Human infections are acquired by contact with infected animals, consumption of contaminated unpasteurized dairy products, and through improper laboratory handling (inhalation and cutaneous exposure). Over 500,000 cases are reported worldwide annually. The disease is frequently a problem in countries that do not have good standardized and effective public health and domestic animal health programs. The incidence is lower in the United States (100 to 200 cases annually), although cases are reported from California and Texas, and by residents and visitors from Mexico.

Depending on the species, human brucellosis causes a range of symptoms. Acute disease has an onset of up to 2 months. Initial symptoms are nonspecific and consist of fever, sweating, headache, back pain, and malaise. Cutaneous, neurologic, and cardiovascular complications characterize severe infections. Chronic complications involve recurrent fevers, joint pain, and fatigue.

Treatment with doxycycline and rifampin in combination for 6 weeks prevents recurring infections. Timing of treatment and severity of illness dictates the length of the recovery period, which lasts from several weeks to several months. Although the mortality rate is low (<2%), the lack of an effective human vaccine makes this organism more difficult to prevent mass dissemination and infection.

Salmonellosis (*Salmonella* species)

Salmonellosis is caused by infection with *Salmonella* species, a gram-negative bacillus. It is a member of the Enterobacteriacea family that colonizes the GI tracts of many species of animals, including chickens, cattle, and reptiles. Because of the large number of reactions that salmonella display against human antibodies, over 2400 known serogroups have been classified into 3 pathological categories. These include: (1) salmonella that are highly adapted to human hosts, such as *S. typhi* (Group D) and *S. paratyphi* (Group A), which produce typhoid fever and paratyphoid fever, respectively; (2) salmonella that are adapted to nonhuman hosts that cause disease almost exclusively in animals; and (3) salmonella that are not adapted to specific hosts and involve the majority of the 2200 serotypes, designated *S. enteritidis* (Group D non-typhoidal salmonella). Infections with species of *S. enteritidis* account for 85% of all salmonella infections in the United States (typhoid fever infections caused by *S. typhi* are rare, with only 400 to 500 cases reported annually).

Approximately 1.4 million cases of salmonellosis infections occur in the United States annually as a result of fecal-oral transmission by direct or indirect contact with animals, foodstuffs, and excretions from infected animals or humans. Gastroenteritis results primarily from infection with group D nontyphoidal salmonella. Symptoms usually start 12 to 48 hours after ingestion of

the organisms, with nausea and mild to severe abdominal pain, followed by watery diarrhea, sudden fever, and sometimes vomiting and dehydration. Nontyphoidal salmonellosis is usually mild to moderate, self-limiting, lasts 4 to 7 days, and has a mortality rate of less than 1%. A chronic carrier state is possible, but is more common in cases of typhoid fever. Chronic carriers shed organisms in the stools for at least a month. Therefore, food handlers who have been infected pose a serious epidemic risk.

Occasionally, more severe, protracted illness and long-term consequences result from salmonella poisoning including: (1) enteric fever, (2) focal (localized) infections, and (3) bacteremia. Enteric fever is a systemic syndrome manifested by fever, prostration, and bacteremia. Enteric fever is attributable primarily to group B, S. typhi, and with milder group A, S. paratyphi, referred to as parathyphoid fever (see below). Focal infections of infected organs start in the gastrointestinal tract and disseminate to the liver, gall bladder, and appendix. Bacteremia, characterized by sustained septicemia with *S. typhi*, *S. paratyphi*, *S. choleraesuis*, and *S. enteritidis*, is relatively uncommon in patients with gastroenteritis.

Other routes of contagion include ingestion of poorly cooked meat and handling of raw infected meat. Unsuspected ingestion of contaminated, poorly cooked poultry, raw milk, or eggs or egg products, are often the perpetrators (the eggs may be contaminated both on their surface and within). Outbreaks are more common in summer months and are often related to contaminated egg salad or chicken salad.

There is no acceptable antibiotic cure for uncomplicated nontyphoidal salmonellosis. Gastroenteritis is treated symptomatically with fluids, electrolytes, and a bland diet (for dehydration and continuous fever). Antibiotics prolong excretion of the organism and are unwarranted in uncomplicated cases. Antibiotic resistance is more common with nontyphoidal salmonella than with *S. typhi*. In addition, antibiotics can prolong the shedding of organisms in the stools after the drug has been discontinued.

As with brucellosis, the lack of an effective vaccine warrants concern that salmonella can be used as a possible bioterrorist tool. Epidemiologically, preventing contamination of foodstuffs by infected humans is paramount. Contaminated raw eggs may be unknowingly ingested by eating such foods as salad dressings, homemade ice cream, mayonnaise, cookie dough, and frostings. Ready-to-eat food, raw food, fruits, vegetables, or prepared desserts must be properly cooked, handled, stored, and/or refrigerated. Hand washing is essential before handling any food and in between handling different food items. It is easy to observe how direct, deliberate, or inadvertent contamination can occur in the absence of proper hygienic food handling measures.

Typhoid Fever

Typhoid fever is a less common, yet life-threatening, infection caused by *Salmonella typhi*. About 400 cases occur each year in the United States through fecal-oral transmission, of which 70% are acquired while traveling internationally. It affects about 12.5 million persons each year in the developing world. The organism is responsible for enteric fever. After 10 to 14 days incubation, gradually increasing nonspecific fever, headache, myalgias, malaise, and anorexia develop and persist for about 1 week, along with GI symptoms. The cycle continues with bacteremia and colonization of the gallbladder, and reinfection of the intestinal tract. The disease is usually treated with antibiotics (fluoroquinolones, chloramphenicol, gentamicin, trimethoprim/sulfamethoxazole, or broad-spectrum cephalosporins), but vaccination is recommended, especially for travelers to endemic areas. Complications of untreated typhoid fever are associated with a 20% mortality rate.

Escherichia coli O157:H7

This gram-negative enteropathogenic bacteria is an emerging cause of foodborne illness. The Escherichia genus consists of 5 species of which *E coli* is the most common and clinically important. Approximately 73,000 cases of infection occur annually in the United States. *E coli* possesses a broad range of virulence factors, exotoxins, and adhesion molecules, allowing the organism to attach to the GI and urinary tracts.

A large number of enteropathogenic groups of *E coli* inhabit the small and large intestines of healthy cattle and are further classified according to their serologic serotypes. Most *E coli* strains are part of the normal human bacterial flora. *E coli* serotype *O157:H7*, however, is not. In fact it is one of the most virulent strains, responsible for producing fatal enterotoxins, which are responsible for sepsis and urinary tract infections. It is also a prominent cause of neonatal meningitis and gastroenteritis in developing nations. Strains of pathogenic *E coli* are subdivided into 6 groups: enterotoxigenic, enteropathogenic, enteroinvasive, enterohemorrhagic, enteroaggregative, and diffuse aggregative. Each causes a variety of diseases including traveler's and infant diarrhea, dysentery, intra-abdominal infections, hemolytic uremic syndrome, and hemorrhagic colitis.

The organism's ability to invade intestinal epithelial cells, its capacity to release exotoxins, and its ability to express adhesion molecules, confers the properties nec-

essary for producing gastroenteritis. The disease is characterized by acute dysentery accompanied by abdominal cramps with little or no fever.

Infection is acquired through ingestion of poorly cooked ground beef, consumption of lettuce, salami, or unpasteurized milk or juice, or contact with cattle excrement. Waterborne transmission occurs through swimming in contaminated lakes or pools, or drinking inadequately chlorinated water. The organism is easily transmitted from person to person and has been difficult to control in child day-care centers. With the exception of severe complications, most infections are self-limiting and last 5 to 10 days. Antibiotic treatment is unwarranted and may actually precipitate kidney infections. Antidiarrheal agents, such as loperamide, should also be avoided.

Thorough cooking and proper handling of ground beef and hamburger are effective in preventing *E coli* infections. Raw meat should be kept separate from ready-to-eat foods. Hands, counters, and utensils should be washed with hot soapy water after they contact raw meat. Drinking unpasteurized milk, juice, or cider should be avoided. Fruits and vegetables should be washed thoroughly to avoid exposure.

Cholera (*Vibrio cholerae*)

Cholera is an acute, diarrheal illness caused by intestinal infection with the gram-negative anaerobic bacterium *Vibrio cholerae*. The species are subdivided into over 200 serogroups on the basis of their somatic O antigens. *V. cholerae* serogroup O1 or O139 is responsible for classic epidemic cholera and it produces cholera toxin.

Although the infection is often mild or asymptomatic, approximately 1 in 20 infected persons has severe disease, which is primarily due to the secretion of the toxin. The cholera toxin is similar to the heat-labile enterotoxin of *E coli*; during infection, it stimulates intestinal hypersecretion of water and electrolytes. Within 2 to 3 days of ingestion, copious watery diarrhea, vomiting, rapid loss of body fluids, and leg cramps develop. The symptoms eventually progress to dehydration, metabolic acidosis, shock, and cardiovascular collapse. If untreated, the condition is fatal in 25% to 50% of cases.

Like other enterobacteria, cholera is acquired by ingesting contaminated water or food. Large epidemic outbreaks are related to fecal contamination of water supplies or street vended foods. The organism is occasionally transmitted through eating raw or undercooked shellfish that are naturally contaminated. Although risk is extremely low (1 per million), even in travelers, it is a major cause of epidemic diarrhea throughout the developing world. A few cases have occurred in the United States among persons who traveled to South America or ate contaminated food brought back by travelers to that region.

Fluid and electrolyte replacement is effective in preventing death, but the logistics of delivery in remote areas during pandemics renders this option difficult to achieve. Doxycycline, trimethoprim-sulfamethoxazole, and furazolidone reduce the bacterial burden and toxin production. Because of advanced water and sanitation systems, cholera is easily prevented and treated and is not a major threat in industrialized nations. Currently available killed parenteral vaccines offer incomplete protection of relatively short duration; thus, their use has been discontinued.

Smallpox

Naturally occurring smallpox (*variola major*) is a member of the orthopoxvirus family, the largest and most complex family of viruses. It is easily transmissible via close person-to-person contact. The virus accounted for 7% to 12% of all deaths in 18th century England. The last case of smallpox in the United States occurred in 1949, and the last in the world occurred in Somalia in 1977. Routine vaccination in the United States was stopped in 1971; the World Health Organization (WHO) determined in 1980 that smallpox had been successfully eradicated.[11]

Smallpox virus is inhaled and replicated in the respiratory tract. Dissemination occurs via lymphatics, resulting in viremia. The lymphatic vessels provide the pathways for the virus to spread to the spleen, bone marrow, liver, and skin (characteristic rash). A second viremia causes the development of additional lesions. Depending on which of the 2 variants of smallpox is contracted, mortality ranges from 15% to 40% (for *variola major*) to 1% (*variola minor*).

The incubation period for *variola* is about 7 to 17 days. Initial symptoms include high fever, fatigue, and head and back aches. The characteristic lesions (pocks) appear in 2 to 3 days on the face, arms, and legs. Lesions become pus-filled and begin to crust early in the second week. Eschars develop, separate, and slough off after 3 to 4 weeks.

Smallpox is very contagious through the respiratory/salivary route. Individuals are most contagious during the first week of signs and symptoms, corresponding to high viremic periods. Smallpox now only infects humans through accidental or occupational exposure.

Although routine vaccination against smallpox ended in 1972, the level of continuous immunity among persons vaccinated before 1972 is uncertain. Recently, the threat that smallpox could be used as a weapon of bioterrorism has prompted the development of new vaccination strategies for both military personnel and civil-

ians. *Vaccinia*, a form of cowpox, is used for the production of smallpox vaccine. The procedure consists of scratching live virus into the patient's skin and observing for the formation of vesicle and pustules. Complications and potential risks related to vaccination occur primarily in immunocompromised individuals and, more recently, in persons with preexisting cardiovascular disorders. The most serious complications are encephalitis, progressive infection (*vaccinia necrosum*), and myocardial infarction.

Viral Hemorrhagic Fevers

Viral hemorrhagic fevers (VHF) are a clinically related group of viral diseases with a diverse etiology.[12] The family of Filoviridae include the Marburg and Ebola viruses. Similarly, the family of Bunyaviridae include the genuses *hantavirus and bunyavirus* (primarily responsible for causing encephalitis in humans). All are RNA viruses endemic in Africa and, with the exception of the bunyavirus, cause severe or fatal hemorrhagic fevers. The condition is characterized by acute onset of fever, headache, generalized myalgia, conjunctivitis, and severe prostration, followed by various hemorrhagic symptoms. The organism facilitates the destruction of endothelial cells leading to vascular injury and increased capillary permeability. Antiviral therapy has not shown to be clinically useful.

Arenaviruses, including the Lassa fever virus, Junin, and Machupo viruses, are endemic in Africa and South America. The organisms stimulate cell-mediated inflammatory responses following an incubation period of 10 to 14 days. The syndrome is manifested by fever, petechiae, cardiac, hepatic, and splenic damage. The recently approved antiviral drug, ribavirin, has demonstrated some activity against Lassa fever, which has a 50% mortality rate if untreated.

CHEMICAL AGENTS AS THREATS TO PUBLIC SAFETY

Nerve Gases

The nerve gases were developed during World War II as possible chemical warfare agents, the first compound of which was tetraethyl pyrophosphate (TEPP, see Table 2).[13] The nerve gases, such as sarin (GB), tabun (GA), and soman (GD), all of which are phosphonofluoridic acid esters, are similar to, but more toxic than the organophosphate (OP) insecticides. The clear, colorless, tasteless liquids inhibit the action of acetylcholine esterase (Ach-E) by forming an irreversible OP–Ach-E complex, rendering it incapable of hydrolyzing acetylcholine (Ach). Inhibition of the enzyme results in accumulation and overstimulation of Ach at autonomic and somatic receptors. Excessive stimulation of nicotinic receptors is followed by skeletal muscle paralysis. These circumstances account for the toxic manifestations of OP insecticides as well as the nerve gases.

The compounds are miscible with organic solvents and water, and readily absorbed through skin. Soman is the most toxic of the 3 "G" agents and one of the most toxic compounds ever synthesized, with fatalities occurring in humans with an oral dose of 10 µg/kg. Recently, however, VX (methylphosphonothioic acid ester) has emerged as a more toxic nerve agent. Unlike more volatile aromatic and aliphatic hydrocarbons, VX is a more stable compound. Heating VX liquid renders it to a gaseous form that is more easily handled as a terrorist weapon, transmitted to victims through inhalation or dermal or ocular contact with airborne vapors. Contamination of food and water supplies is also possible. Of concern is its ability to accumulate in physiological compartments, its slow metabolic degradation, and its high density, enabling it to spread throughout low-lying areas.

Onset of symptoms depends on route of exposure (seconds for inhalation of vapors, hours for dermal or oral exposure). As with all the nerve agents, VX produces a severe cholinergic syndrome, terminating in convulsions, respiratory failure, and death. Recovery from mild or moderate exposure to a nerve agent is possible. Treatment relies on removal from the source of exposure, supportive measures, decontamination, and rapid administration of atropine (antimuscarinic) and pralidoxime chloride (Ach-E reactivator). The FDA has recently approved pyridostigmine bromide, an anticholinesterase agent, as a prophylactic drug for United States military personnel to increase survival rates after exposure to soman poisoning during combat use.

Vesicants, Chemical Asphyxiants, Pulmonary Irritants

Vesicants, such as nitrogen mustard compounds, are capable of causing tissue necrosis. These alkylating agents have a delayed onset of action (about 6 to 8 hours), although cellular necrosis ensues immediately. Inhalation produces a typical pulmonary irritation. Sulfur mustard compounds (ie, "mustard gas") possess a garlic odor, although they are sometimes odorless. The compounds are generally colorless or yellowish liquids, do not accumulate in the environment, and are not a threat for accidental public exposure.

Lacrimating agents (benzyl bromide), simple asphyxiants (inert gases), chemical asphyxiants (carbon monoxide, cyanide), and pulmonary irritants (carbon disulfide, phosgene), are now recognized as potential chemical bioterrorist threats. The clinical toxicity of these compounds is discussed in detail in other lectures.

Ricin (*Ricinus communis*)

Ricin is derived from the processing of the castor bean and its seeds (Euphorbiaceae) in the extraction of castor oil. Containing one of the most potent toxins, the plant is indigenous to temperate and tropical India, Africa, and South America. The oil apparently had only technical uses until the 18th century when its medicinal application was explored.[14] Ricin is composed of 2 lectins found in the seeds, ricin I and II. The compounds, especially ricin II, bind to and inactivate the 60S ribosomal subunit in somatic cells, thus blocking protein synthesis. The potent cholinergic properties of the oil have rendered it useful for decades as a nonprescription laxative.

Ingestion of intact castor bean seeds is unlikely to cause deleterious effects for several days; ingestion of chewed castor beans rarely results in significant morbidity. Gradually, however, it produces nausea, vomiting, dyspnea, and diarrhea. Gastroenteritis follows and is characterized by severe bloody diarrhea, vomiting, and dehydration. Mental confusion, seizures, and hyperthermia complicate the scenario.

Inhalation of ricin powder usually produces a cough, dyspnea, nausea, and vomiting within a few hours. Pulmonary congestion and cyanosis can follow. Injection of a lethal amount of ricin (about 500 μg) would first cause local muscle paralysis and lymph node necrosis near the injection site. Massive stomach and intestinal hemorrhaging would ensue, followed by multiple organ failure. Death occurs within 36–48 hours and is due to focal necrosis of the liver, spleen, lymph nodes, intestine, and stomach.

Ricin is otherwise not an environmental metabolic product and unintentional ricin poisoning is highly unlikely. Its presence therefore suggests deliberate contamination. The manufactured material can be dissolved in water, vaporized, or injected, thus facilitating its exposure through oral, respiratory, or parenteral routes.

Antidotes are not available for ricin poisoning. Treatment necessitates supportive emergency measures, including maintenance of respiration and renal perfusion, and gastric decontamination.

INSTRUCTIONAL METHODS AND CONTENT

One of the main goals of any lecture is to maintain the students' attention and focus. To accomplish this, the lecture must be, to some extent, entertaining. Several methods, alone and in combination, are used to present the material to ensure the students' attention and to help them retain the information. For instance, the lectures routinely incorporate clinical examples from professional experience. The students are better able to relate to these examples, principally because the scenarios are "reality-based" experiences and not simply drawn from the literature. In fact, case studies, guest speakers, or hands-on demonstrations are rarely used. Also, when presenting review material of general physiology or microbiology, examples of pharmacologic and toxicologic agents are inserted, especially when the chemical mechanism of the compound fits directly into the discussion. Inclusion of applicable instances from current events is also used as a tool for prompting the student to relate the lecture material to a practical situation. Since bioterrorism is often a topic of the headline news reports, it is not difficult to insert examples from current events into the classroom discussion. Lecturers might have to be more creative when attempting to apply news events to other lecture topics.

All lectures are available as Microsoft *PowerPoint* presentations online prior to the scheduled class. Students are encouraged to print the outlines for use during class lecture. The presentations, however, are not detailed instructor's notes, nor are they as extensive as presented in this manuscript. In fact, most lectures are simply outlines of the class presentations, thus requiring that the students actively participate in class by taking their own notes. This requires good note-taking skills and coordination of the notes with assigned text readings; competencies that are developed with experience and with the help of student services. Consequently, a good set of notes, proper study habits, and completion of the reading assignments constitutes customary preparation for the examinations.

Multiple-choice examinations alone may not be the best instruments for assessing academic performance. Nevertheless, examinations can be constructed fairly and factually, and are designed to test the student's ability to retain and/or understand the information. Prior to examinations, online chat sessions have been useful in gauging students' level of comprehension. The first sessions are initially headed by the instructor; subsequent sessions, if necessary, are initiated by proactive students. The purpose of the sessions is not only for instructors to answer questions prior to the examination, but also for the instructor to become more aware of students' level of understanding. A series of practice questions placed online prior to the examinations also helps students gauge their level of understanding and the effort needed as follow-up. Subsequent to the examinations, test reviewing is essential. Whether performed in class or individually in the office, this is an opportunity for the student to determine the reasons for misguided answers. A suitable approach to solving the problem is then forthcoming.

Other tools that are incorporated during the lecture to maintain students' attention include adherence to a rigorous curriculum and fastidious attention to details. There is no greater insult to a person's intelligence than expecting less than their potential.

There is no substitute for creating a welcoming environment in the classroom. Speaking to students as individuals rather than as an assembled herd, showing compassion yet remaining firm, displaying understanding yet showing fairness, conveying encouragement while preserving rigorous standards; these attributes convey the instructor's personal enthusiasm for the subject and demonstrate concern for the students' academic progress. Maintaining a sense of humor also promotes the instructor's self-awareness of the global view of the subject. Finally, as a rule, there are no lengthy tutoring sessions outside of class time, no jokes during lectures, and never any extra projects for individual students that have not been assigned to the entire class.

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REFERENCES

1. Clinical and Biological Threats to Public Safety. In: Barile FA. *Clinical Toxicology: Principles and Mechanisms*. Boca Raton, Fla: CRC Press; 2004:397-412.
2. Centers for Disease Control and Prevention. Public Health Emergency Preparedness and Response. Available at: http://www.bt.cdc.gov. Accessed April 19, 2004.
3. Rosenbloom M, Leikin JB, Vogel SN, Chaudry ZA. Biological and chemical agents: a brief synopsis. *Am J Ther*. 2002;9:5-14.
4. Slater LN, Greenfield RA. Biological toxins as potential agents of bioterrorism. *J Okla State Med Assoc*. 2003;96:73-76.
5. Franz DR, Zajtchuk R. Biological terrorism: understanding the threat, preparation, and medical response. *Dis Month*. 2002;48:493-564.
6. Broad WJ, Miller J. Threats and responses: the bioterror threat; health data monitored for bioterror warning. *New York Times, National Desk*. Section A, Page 1, January 27, 2003.
7. Bozeman WP, Dilbero D, Schauben JL. Biologic and chemical weapons of mass destruction. *Emerg Med Clin North Am*. 2002;20:975-993.
8. Terriff CM, Schwartz MD, Lomaestro BM. Bioterrorism: pivotal clinical issues. Consensus review of the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2003;23:274-290.
9. *USAMRIID's Medical Management of Biological Casualties Handbook*. US Army Medical Research Institute of Infectious Diseases, Centers for Disease Control and Prevention; 2003.
10. Orloski KA, Lathrop SL. Plague: a veterinary perspective. *J Am Vet Med Assoc*. 2003;222:444-448.
11. Drazen JM. Perspective: Smallpox and Bioterrorism. *N Engl J Med*. 2002;346:1262-1263.
12. Lashley FR. Factors contributing to the occurrence of emerging infectious diseases. *Biol Res Nurs*. 2003;4:258-267.
13. Agency for Toxic Substances and Disease Registry (ATSDR). *Toxicological Profile for Mustard Gas*. Draft for Public Comment. Atlanta, Ga: US Department of Health and Human Services, Public Health Service; 2001.
14. Olsnes S, Kozlov JV. Ricin. *Toxicon*. 2001;39:1723-1728.