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Protection from Bioterror and Biological Warfare Agents

By Prof. Garth L. Nicolson
The Institute for Molecular Medicine (www.immed.org)
Huntington Beach, California 92649

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Bioterror and Biological Warfare agents are most often colorless, by-and-large odorless microorganisms (bacteria, viruses, fungi) or toxins (usually protein toxins) derived from microorganisms that can be spread in air as aerosols or in food or drink to infect as many people as possible. They are easily concealed, and thus difficult to detect before an attack. They are also difficult to detect when released, so a biowarfare or bioterror attack would be difficult to ascertain, especially due to the usually nondescript initial signs and symptoms expected in casualties from such an attack. Their main advantages to terrorists are allowing easy escape and causing panic and chaos within a civilian population. Their aim is to overwhelm emergency medical departments at local hospitals and clinics. However, there are ways to help protect yourself against bioterror agents and by extrapolation biological warfare agents and to help identify an attack when it occurs.

Terror not Casualties is the Objective

The most likely target for bioterrorism is a major city or other densely crowded areas, such as transportation hubs, major sports events or public rallies and especially government buildings. Although recently even civilians in remote areas were frightened enough to seek medical attention for what they perceived was a bioterror attack, in reality an attack in a remote area would be extremely unlikely. In high population density areas, the ventilation systems in large buildings might be especially temping targets, as these are rarely protected. As we have seen, practically any delivery system can be used to penetrate an office building, even a letter delivered by the postal service. Once an attack has occurred, most biological agents (see below) would need an incubation period of several days in order to cause sickness. As mentioned above, this has the advantage of allowing a bioterrorist time to escape or perform undetected other acts of terrorism. Thus a single bioterrorist could 'hit' several targets long before an attack was suspected. Even with large numbers of people exhibiting nonspecific signs and symptoms within a few days after an attack, it would take some time for the medical community to recognize these events as a bioterror attack. This is primarily due to the expected dispersed nature of patients seeking medical attention at different institutions and at different times.

The recent outbreak of inhalation anthrax in Florida and cutaneous anthrax in New York in the first week of October 2001 might be an example of a fairly restricted bioterror attack. In this case a very modest amount of anthrax spores caused only a few casualties and one death but caused tremendous panic in the local populous. Early reports from government agencies were directed at restoring public confidence by reassuring people that this was an isolated incident and denying that a potential bioterror attack had even occurred. Later authorities had to admit that an

attack had indeed occurred. The lesion was that we should not expect authorities to be immediately candid about a bioterror attack.

Bioterrorism does not have to cause large numbers of immediate deaths to be effective. Most biological agents do not cause widespread immediate fatalities, or even large numbers of deaths within days of exposure, and most exposed patients might not even have a life-threatening disease. The main functions of bioterrorism are to cause panic, disruption and chaos, so biological agents don't have to cause a fatal disease to be effective. In fact, many biological warfare agents are categorized as 'incapacitating agents' that are not intended to produce a fatal disease (Table 1). They are more effective if they incapacitate and produce strain on a health care system by having many thousands of sick patients inundate treatment facilities that contain only limited quantities of drugs and only a few isolation beds. Also, it is much easier to spread an incapacitating agent from person to person, because it would not cause enough alarm to require quarantining of exposed persons, which could limit additional exposures. Recent Ebola virus outbreaks in the Congo suggest that the most effective method to limit casualties is to quickly quarantine anyone who shows signs and symptoms of hemorrhagic fever. Incapacitating agents often have relatively long incubation times, allowing their widespread penetration into a population before they are ever diagnosed. Thus exposed individuals may bring the agent back 'home' to an unsuspecting family member and spread the disease further. This may have happened to veterans with chronic infections, such as *Mycoplasma* and *Brucella* infections, who returned from the Gulf War only to slowly spread their chronic illnesses to spouses and children.

Biological Agents and Bioterrorism

There are several types of biological agents that could be useful for bioterrorism. First, there are lethal agents, such as the Ebola, Lassa and other viruses that cause viral hemorrhagic fever, inhalation anthrax caused by *Bacillus anthracis* spores, smallpox virus, pneumonic plague caused by *Yersinia pestis* or purified protein toxins, such as the *Ricinus communis* toxin ricin or *Clostridium botulinum* toxin (Table 1). In addition, there are incapacitating agents that cause brucellosis, mediated by *Brucella* species, Q fever caused by *Coxiella burnetii*, tularemia caused by *Francisella tularensis*, mycoplasmal infections caused by *Mycoplasma fermentans* and mold toxins, such as the T2 mycotoxin. As mentioned above, incapacitating agents for the most part cause chronic illnesses that are not usually fatal. However, these illnesses can cause tremendous chronic health problems in infected patients, and most are contagious and the disease could spread and eventually cause an epidemic of chronic illnesses.

Table 1. Some Common Biological Warfare Agents that Can be Used for Bioterrorism

Disease or agent	*Lethality (death)*	*Incubation period*	*Effective dose*	*Environmental stability*
Lethal Agents				
Anthrax	high	1-6 d	10,000-50,000 spores	very stable for years
Plague	high	1-6 d	100-500 organisms	stable for 1 year

Smallpox	high	7-17 d	10-100 organisms	very stable
Ebola virus	high	2-6 d	10-100 organisms	unstable
Botulism	high	1-5 d	0.001 mcg/Kg weight	relatively stable
Ricin	high	1-2 d	3-5 mcg/Kg weight	stable
Cholera	high	1-3 d	10-500 organisms	unstable
Incapacitating Agents				
Brucellosis	low	months	10-100 organisms	very stable
Tularemia	low	2-15 d	10-50 organisms	stable for months
Q fever	low	15-40 d	1-10 organisms	stable for months
Mycoplasma	low	months	10-100 organisms	moderately stable
T-2 Mycotoxins	moderate	1 d	unknown	very stable
Type B Enterotoxin	moderate	<1 d	0.03 mcg	moderately stable
Equine encephalitis	low	2-6 d	10-100 organisms	relatively unstable

Many of the most lethal biological agents, such as the hemorrhagic fever viruses, are quite unstable in the environment due to their susceptibility to sunlight and extreme temperatures and would not be effective if deployed in an aerosol at long range, for example, by aircraft sprayers. Most viruses that would be useful as bioterror agent quickly cause unique signs and symptoms that would allow isolation of the victims and thus prevent further spread of the disease. Many of the bacterial or viral incapacitating agents, however, slowly produce illnesses that would not be noticeable until some time later, and during this period they could be slowly and unknowingly spread to others. Official denial helps this process and allows further penetration into the population. For example, the widespread official denial of biological exposures during the Gulf War, I believe, helped spread chronic infections, such as *Mycoplasma fermentans*, that we and others after us found in a rather large subset (~40%) of Gulf War Illness patients. The continuing denial by the medical organizations that would be expected to respond to such outbreaks is not comforting, because these are the same organizations that would be responsible for responding to a bioterror attack. Thus if an attack is obvious and results in immediate fatalities, we could expect an all out response. On the other hand, if an attack is not immediately obvious, such as would be expected if incapacitating agents were used, we might not expect an official response at all, even in the face of continuing casualties and illnesses in the population, and we might expect official denials instead in order to reassure a panicky public.

Diagnosis and Treatment of Biologic Agents

Many agents useful for a bioterror attack, even the lethal agents, produce nonspecific clinical signs and symptoms, so it is important to be aware of these if many casualties occur within a short period of time in one location. Public health officials are being trained to spot these 'clusters' of illness and take appropriate action. Unfortunately, in an era of managed health care, few hospitals and clinics probably have bioterrorism emergency plans in place. There has been some national planning for bioterror attacks, and regional emergency supplies and personnel have been placed at the disposal of public health officials. This plan can be relatively effective for the lethal agents listed in Table 1, but they probably won't be effective if incapacitating agents are used. The gradual appearance of casualties with chronic signs and symptoms would probably not be recognized by public health officials.

When detected early, most of the biological agents listed in Table 1, even some of the most lethal agents, can be effectively treated with antibiotics or antivirals. However, an attack may go unnoticed for some time, and it might take some fatalities before public health officials notice that an attack may have occurred. There is a strategic national stockpile of antibiotics and antivirals tailored for bioterror attacks, and it can be deployed anywhere in the United States within 12 hours of a documented attack. Thus it is probably not necessary to stock antibiotics and antivirals, some of which can be quite expensive, in anticipation of an attack. However, having on hand modest amounts of certain antibiotics that can be taken as soon as certain signs and symptoms occur could save your life. If a terrorist group has the latest information and advanced expertise to produce resistant variants of biological agents, they could produce bacteria and viruses that can withstand the standard antibiotics and antivirals used for treatment. Although this scenario is considered unlikely, it could pose some potential problems for treatment of attack victims. For most agents there are alternative drugs that can be used. Although some of these are not as effective as the first line treatments, they should be adequate for most patients. In addition, there are steps that can be taken to increase that chance of survival of a biological attack. These will be discussed below.

The Signs and Symptoms of Some Biological Agents

Most bioterror agents do not cause unique clinical signs and symptoms that are immediately recognizable in exposed individuals. This would defeat the purpose of a bioterror attack if the means were immediately known. Also, if the bioterror agent is quite obvious, then preventive treatment can begin immediately in people who were in close proximity but do not yet show any clinical symptoms. The most common form of agent that could be used for a bioterror attack are bacteria. Since bacteria are susceptible to antibiotics, especially in the early phase of the infection, this is an appropriate approach to counter a bioterror attack. However, not all of the agents that could be deployed are bacterial. Some examples of the most likely agents that might be used in a bioterror attack are listed in Table 1 and below:

Anthrax. The most dangerous biological agent is probably the spore form of *Bacillus anthracis*. Although the inhalation of anthrax spores is uniformly and rapidly fatal, anthrax infection can be successfully treated in its early stages with antibiotics like doxycycline or ciprofloxacin. Victims of an inhalation anthrax attack will present initially with a flu-like illness with malaise, dry

cough and mild fever. This phase of the disease usually takes a few days, followed by severe respiratory distress. Anthrax can be treated, but only before it enters the severe respiratory distress phase. Most patients in the severe systemic phase will die with or without antibiotic treatments and usually before a laboratory diagnosis can confirm the presence of the bacterium in blood and tissues. There is a vaccine available, but there are many problems with this vaccine, as we have documented with the military's anthrax vaccine program (see more information on this vaccine under Gulf War Illnesses section of our website, www.immed.org). We do not consider this vaccine safe for civilian use, and it would have to be administered in several doses over a period of 18 months to 2 years before an attack. On the other hand, chemoprophylactic use of antibiotics has been shown to be effective in preventing the illness in 80-90% of monkeys given anthrax spores by inhalation. If a terrorist group uses a form of anthrax that is resistant to the commonly used antibiotics, then others are available but time may prevent their effective use. Persons that come into direct contact with anthrax spores should wash thoroughly with soap and water and store their clothing in a sealed plastic bag for biohazard disposal. If anthrax spores enter the skin, cutaneous anthrax infection can occur, resulting in a black scab over the contaminated area. At this point the infection remains treatable with antibiotics, but if left untreated approximately 20% of cases result in death. Persons with cutaneous anthrax can also have headaches, muscle aches, fever, nausea and vomiting, indicating a systemic form of the infection. Ingestion of contaminated meat can also result in infection (gastrointestinal anthrax). If left untreated, this form can result in 25-60% fatalities. Gastrointestinal anthrax can produce intestinal bleeding and similar signs and symptoms to systemic forms of the disease. Person-to-person transmission of *Bacillus anthracis* is poor, and this type of infection is not considered contagious.

Hemorrhagic fever viruses. Viral hemorrhagic fevers caused by Ebola, Marburg, Lassa or Bolivian Hemorrhagic Virus are rapidly progressing diseases that show extremely high mortality rates. Many of these infections are caused naturally by contact with contaminated food, but they can also occur by contact with urine, feces or saliva. The viruses are fairly fragile, and dispersing them as an aerosol would not be expected to maintain their viability for long periods of time. Patients usually present with high fever, muscle aches and pain, hypotension and prostration. In severe cases, patients have signs of disseminated vascular coagulation with signs of mucous membrane hemorrhage and shock. At this stage the disease is almost always fatal. For some hemorrhagic fever viruses the antiviral ribavirin offers some benefit. Patients require immediate fluid, plasma or blood support. Although these viruses are airborne, person-to-person transmission can be for the most part prevented by wearing gowns, gloves and marks. Fortunately, these viruses do not persist in the environment for long periods, and most outbreaks in Africa have been limited by immediately isolating patients.

Plague. Plague is caused by the bacterium *Yersinia pestis*, which is usually spread from rodents to man through the bites of infected fleas or other insects. In a bioterror attack the bacterium could be spread by inhalation of droplets containing *Y. pestis* or terrorists could simply disseminate infected fleas or other biting insects. If left untreated, inhalation of *Y. pestis* is nearly always fatal within 2-3 days. Patients usually suffer severe pneumonia with malaise, high fever, cough, spitting up blood and labored breathing. Eventually patients go into septic shock and die because of respiratory failure and circulatory collapse. Respiratory plague is very contagious, and strict isolation is necessary. Early treatment with antibiotics, such as

doxycycline, ciprofloxacin or other antibiotics, at the first appearance of signs and symptoms is crucial for survival. There is a vaccine available, but immunization requires several vaccinations and boosters.

Botulism. Botulism is caused by toxins released from the bacillus bacterium *Clostridium botulinum*. This can occur naturally by ingestion of infected foods, but a terrorist attack may utilize an aerosol of the bacterium or the purified toxins. The botulism toxins are neurotoxins and cause characteristic neurological signs and symptoms within 1-5 days, such as dry mouth, double vision, excessive pupil dilatation, local paralysis, and difficulty in swallowing. The neurotoxins usually do not cause a fever, and patients are alert and oriented. Most patients die of respiratory failure, so respiratory support is essential and may have to be continued for several weeks to months. The toxin can be removed from skin by washing with soap and water. Clothes must be placed in a sealed plastic bag for biohazard disposal. If the toxin is used, there is no danger of transmission from infected patients. Although an antitoxin is available, it is only effective in preventing further progression; it cannot reverse neurological damage that has occurred.

Smallpox. Smallpox is caused by the naturally occurring Variola Virus. After exposure, the incubation period for smallpox is approximately 7-17 days, average 12 days, during which nonspecific signs and symptoms, such as fever, malaise and aches occur within a few days. Characteristic rashes develop, starting as papules that progress to vesicles and then pustules that can form scabs in 1-2 weeks. At this stage the disease can be mistaken for chicken pox, and it can be spread to others, so quarantine is important for anyone who has direct contact with a patient. About 40% of unvaccinated people will die of smallpox but most people in the U.S. have received some earlier form of smallpox vaccine which should give some protection. The antiviral cidofovir has been used to treat smallpox infections. Effective vaccines are available but were produced many years ago. New vaccines are under development and should be ready within the next year or so.

Brucellosis. Brucellosis is caused by bacteria of the genus *Brucella*. Historically brocellosis was caused by contact with infected livestock or after ingestion of infected milk. Aerosols of *Brucella* are considered very effective at infection. The disease develops slowly over several months as a flu-like infection with nonspecific signs and symptoms, including intermittent fever, chills, night sweats, malaise, muscle pain and soreness, cough and eventually joint pain and soreness, gastrointestinal complaints, nausea, vomiting, diarrhea and constipation. It might be diagnosed as Chronic Fatigue Syndrome or Fibromyalgia Syndrome, but it is rarely fatal. Diagnostic tests are available (see www.immed.org). The suggested treatment is long-term antibiotics, such as doxycycline or rifampin, and immune support.

Mycoplasmas. Pathogenic mycoplasmal infections are caused by several species of mycoplasmas, including *M. fermentans,* among others. These airborne and insect-borne bacterial infections are rarely fatal, but they can cause severe chronic infections that may result in patients being diagnosed with Chronic Fatigue Syndrome, Fibromyalgia Syndrome or Rheumatoid Arthritis. As with brucellosis, the chronic signs and symptoms are many and varied from patient to patient, and testing is available (see www.immed.org). The suggested treatment is long-term antibiotics, such as doxycycline, ciprofloxacin or azithromycin, plus immune support. There is

no known vaccine for mycoplasmas, but individual vaccines have been produced from patient's white blood cells.

Q Fever. Q Fever is caused by the bacterium *Coxiella burnetii*. This can occur naturally from contact with goats, cheep and cattle. The disease develops slowly over a month or more, with fevers, malaise, headache, muscle pain and soreness and other signs and symptoms. About one-half of patients will have a pneumonia with cough and chest pain. In some patients the disease can progress to hepatitis. Treatment includes antibiotics and immune support.

Tularemia. Tularemia or rabbit fever is usually caused by contact with infected animals that carry the bacteria *Francisella tularensis*. It can also be caused by ingestion of contaminated food or water. When aerosols are used as the infective route, the disease that evolves has slightly different signs and symptoms. After an incubation period of 2-10 days, patients present with fever, chills, headache, nausea, vomiting, diarrhea and muscle aches and pains. Many patients will have a pneumonia with coughing. Airborne (person-to-person) transmission can occur but is considered rare. The treatment is a 2-3 week course of antibiotics plus immune support.

Bioterror Attack Preventive and Treatment Procedures

Antibiotics. Since there has been a run on supplies of antibiotics in the United States, is this an effective method to counter a bioterror attack? This would be effective only if there was actual exposure, and the biological agent was bacterial and susceptible to the antibiotic chosen for chemoprophylactic use. In addition, long-term use of antibiotics can have their own problems. Some people cannot take ciprofloxacin because of allergic reactions (hypersensitivity or anaphylactic reactions). For example, ciprofloxacin therapy may result in drug crystals in the urine in rare cases, and patients should be well hydrated to prevent concentration of urine. Adverse antibiotic responses resulted in discontinuing ciprofloxacin in ~3.5% of patients, and such reactions included nausea (5%), diarrhea (2%), vomiting (2%) abdominal pain (1.7%), headache (1.2%) and rash (1.1%). In rare cases cirprofloxacin may cause cardiovascular problems (<1%) and central nervous system (dizziness, insomnia, tremor, confusion, convulsions) and other reactions (<1%). Pregnant women and children should not use this drug due to reduction in bone and cartilage development. Although some practitioners have suggested that lower doses could be used for children, this antibiotic has not been approved for pediatric use. Doxycycline has lower adverse responses and is just as effective against almost all anthrax strains. However, in a few patients doxycycline causes gastrointestinal irritation, anorexia, vomiting, nausea, diarrhea, rashes, mouth dryness, hoarseness and in rare cases hypersensitivity reactions, hemolytic anemia, skin hyper-sensitivity and reduced white blood cell counts. Doxycycline can be used at low dose in children aged 7 and above, mostly because of the chance of tooth discoloration in younger children. Azithromycin is the antibiotic of choice for pediatric cases, but its cost generally prevents widespread use. Adverse antibiotic responses were mild to moderate in clinical trials and included diarrhea (5%), nausea (3%), abdominal pain (3%). In rare cases (<1%) azithromycin may cause cardiovascular problems (palpitations, tachycardia, chest pain) and central nervous system (dizziness, headache, vertigo), allergic (rash, photosensitivity, angioderma), fatigue and other reactions (<1%). In pediatric patients >80% of the adverse responses were gastrointestinal. In children, doses above the suggested 10 mg/kg/day have been shown to produce hearing loss in some patients. Penicillin has been

recommended for some types of bioterror agents, such as anthrax. For example, amoxicillin, a semi-synthetic type of ampicillin, can cause fatal anaphylactic responses in patients allergic to penicillin, gastrointestinal problems (nausea, vomiting, diarrhea and colitis) in some patients, and rarely anemia and changes in white blood cell count. These are usually reversible on discontinuation of therapy. As a relative safe preventive alternative, especially in the absence of a confirmed exposure, immune enhancers have been recommended (see below).

Antivirals. Use of antivirals against viral agents should only be done under the direct care of a physician, and their use is only recommended after a confirmed infection. They are not recommended for chemoprophylactic use due to a relatively high rate of complications and adverse reactions compared to the commonly used antibiotics listed above. Some antivirals have to be given intravenously, and this can only occur in a supervised clinical setting. Cost and availability are factors that severely limit their use, and almost all cannot be used in pregnant women and some cannot be used for children. Certain nutraceutical treatments can be used instead or concurrently, such as Genistein (in soy/red clover) to inhibit viral kinase, rosemary/lemon balm to reduce complement activation, selenite (see below) to inhibit viral replication, barley grass and lauric acid to inhibit lipid metabolism of viruses and *Phyllanthus amarus/niruri* to inhibit viral reverse transcriptase. The efficacy of these supplements in preventing infection by bioterror viral agents is not known.

Vaccines. Specific vaccines can potentially protect against bacterial and viral bioterror agents. Most of these vaccines would have to be administered over a relatively long time period to be effective. For example, the current anthrax vaccine must be administered in multiple doses over an 18-month period to be effective, and it is not even known conclusively that the vaccine is effective against inhalation anthrax. This vaccine is not recommended for civilian use due to the relatively high rate of adverse reactions, including fatalities and autoimmune diseases that have resulted from its use. Other vaccines, such as the smallpox virus vaccine, have been in general civilian use for some time and are relatively safe. New generations of these vaccines are under development, but they will not be available for some time, possibly years.

Passive Immunization. Passive immunization by administration of immune sera containing antibodies against specific bioterror agents is a costly alternative that can only be used after a confirmed exposure. Newer developments include passive immune sera or pure antibodies that can target toxin molecules themselves instead of the microorganisms. For example, antibodies against the anthrax lethal and bloat factors (the lethal toxins) or their protective factor (a transport factor needed to transport the lethal toxins into cells) can potentially stop a fatal form of systemic anthrax. Unfortunately, these approaches are for the most part experimental and are not widely available.

Immune Enhancement and Nutrition. Immune enhancement and nutritional approaches are not expected to be full-proof preventive measures that will protect against bioterror agents. However, a healthy immune system is the first line of defense against microorganisms and may determine the severity of illness caused by infections. Proper nutrition is essential for a healthy immune system. Unfortunately, most people do not have good nutritional habits, and they would be prudent to supplement their diets with certain vitamins (*especially* B-complex, C, E, CoQ-10) and minerals, such as zinc, magnesium, chromium and selenium. Also, patients undergoing

treatment with antibiotics and other substances risk destruction of normal gut flora that provide important digestive enzymes for processing food in the gut. Antibiotic use that depletes normal gut bacteria and can result in over-growth of less desirable bacteria. To supplement bacteria in the gastrointestinal system live cultures of *Lactobacillus acidophilus* in capsules or powder are strongly recommended. A number of natural remedies, such as ginseng root, herbal teas, lemon/olive drink, olive leaf extract with antioxidants fresh or deorderized garlic and oregano oil (in enteric coated capsules), among others, have been shown to be useful for immune support, especially during or after antibiotic therapy. Some additional remedies are: olive leaf extract, lactoferrin and other natural plant products or herbal mixtures. Other important examples of immune support are immune modulators, such as bioactive whey protein, transfer factors and other colostrum-derived products and plant glucans. Good immune boosters have been isolated from mushroom extracts and are widely available from a number of manufacturers. These products have been used to maintain or boost immune systems to prevent infections.

What to do if you Suspect a Bioterror Attack

The most important point to remember if you suspect that you may have been exposed to a bioterror attack is to seek immediate medial attention by going to the Emergency Room at a hospital. Most hospitals have personnel that have been trained to respond to a bioterror attack, and they know what to do to reduce your risk of dying or becoming permanently incapacitated. In contrast to your personal physician, most hospital emergency personnel have received some type of training on how to respond to biological emergencies. Take with you a list of where you have been for the previous several days, who you have come into close contact with, your signs and symptoms and what you think might be the source for your medical problem. Also include any previous medical problems, medications that you are currently on and anything else that would help hospital personnel deal quickly and effectively with your problem. Finally, in the extremely unlikely event that you or a member of your family becomes exposed to a potential bioterror or biological agent, it is important to carefully watch the other members of your family for the appearance of similar signs and symptoms. Speed is of utmost importance in counteracting the agents listed above. It is better to be ridiculed for acting unnecessarily than to not act at all if you feel that you or someone close to you may have been exposed to a biological agent.

For additional information contact:
Prof. Garth Nicolson
President & Chief Scientific Officer
The Institute for Molecular Medicine
Huntington Beach, CA 92649
Email: gnicolson@immed.org

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