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PATHOGENIC PLANT TOXINS AS AN AGENT FOR BIOTERRORISM

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Bioterrorism is a criminal act of deliberate release of virus, bacteria or other germs and agents to cause illness or death of unsuspecting civilians and animals or plants. Bioterror agents are dangerous pathogens which most often are colorless, odorless and tasteless microorganisms or toxins (mostly proteins) derived from microorganisms. These agents are typically found in nature and can be manipulated to increase their pathogenicity, resistance to current medicines and dissemination into the environment. Biological agents can be spread in air as aerosols or in food or water to infect as many people as possible. Biological agents may be used for biological warfare as they are extremely difficult to detect, easily concealed and do not cause illness for several days or months. Many view the potential threat of bioterrorism as a growing one, due to advances in biotechnology, the increased availability of dual use materials and ease of production and transporting biological agents across borders. Compared to resources spent on nuclear and chemical terrorism, relatively little is being done to fight this threat.

Biological Agents and Bioterrorism

There are several types of biological agents that could be useful to bioterrorism. The most common form of agent that could be used for a bioterrorism attack is bacteria. The outbreak of inhalation anthrax in Florida and coetaneous anthrax in New York in Octorber 2001 might be an example of use of bacteria in bioterrorism. Other examples include pneumonic plague caused by *Yersinia pestis* or purified protein toxins such as *Clostridium botulinum* toxin and so on. In addition there other agents that cause brucellosis by *Brucella* species, Q fever caused by *Coxiella bernetti*, tularemia caused by *Francisella tularensis*, mycoplasmal infections caused by *Mycoplasma fermentans* and mold toxins, such as the T2 mycotoxin. The lethal agents like Ebola, Lassa and

other viruses that cause viral hemorrhagic fever (VHF), smallpox virus are to name a few (Table 1-2). Many of these agents are not usually lethal but cause tremendous chronic problems in infected patients, most are highly contagious and could spread and eventually cause an epidemic of chronic illness.

Bioterrorism Agents of Plant Origin & Their Mode of Action

Biotoxins of plant origin may attract terrorists as their use is difficult to be detected early, and their spread is difficult to control. The biotoxins use live organisms to make chemicals. It is important to recognize their leading signs and symptoms. These toxins can be delivered in such ways that they will be inhaled, ingested, or absorbed into the skin. Among biological and chemical agents, the nerve agents aree considered to be the ones likeliest to be used by terrorists.

As many of the plant defense substances are known to be a risk for humans (Hans-Walter Heldt, 2005), it is interesting to study plant metabolites in context of bioterrorism. A number of plant constituents are known that are harmful to humans, e.g., proteins such as lectins, amylase inhibitors, proteinase inhibitors, and cyanogenic glycosides or glucosinolates. In higher concentrations, many plant secondary metabolites are carcinogenic.

There are a huge variety of plant poisons and it is difficult to organize the myriad plant toxins in an understandable manner. Most plant toxins affect more than one organ system in the body, however, it is still helpful to classify plants and their toxins on the basis of their major effect. Table-3 lists many of the known plant toxins, few of which may be worthy of special attention in context of bioterrorism. Knowledge of their mode of action is certainly useful in designing counter-strategies against their possible wide-spread use.

Among known plant toxins, few of those considered most potent are described in some detail below.

Ricin is one of the most potent plant toxins known and the castor plant from which it is derived, *Ricinus communis* (Euphorbiaceae) is ubiquitous. The main producers are India, Brazil and China. The harvesting of castor beans exceeds one million tons annually and ricin is easier to produce than either anthrax or botulinum. As a result, ricin is a convenient, potent and available toxin for terrorist acts (Doan, 2004). Its toxicity is significantly less than that of botulinum toxin; however, it is likelier to be used as a biological weapon because it is not sensitive to heat or cold. The most likely use of this biological toxin would be as a powder, mist or a pellet, but it can also be dissolved in water. However, the chlorination, in municipal water supplies, inactivated ricin. One distinctive feature of ricin poisoning is that its flu-like symptoms are accompanied by fever. As little as 500 µg can be lethal. It is most lethal when inhaled, so that terrorist attacks would most likely occur from a mist or powder. There has been an infamous case of an assassination employing ricin (the Bulgarian writer Georgi Markov in London in 1978).

Ricin kills cells by damaging protein synthesis. Those who survive severe ricin poisoning may still have permanent or long-lasting organ damage. Ricin tricks a cell into turning off a natural deense mechanism that destroys foreign proteins (Tumer, 2008). Ricin inhibits a cell defense mechanism known as unfolded protein response or UPR. A piece of the ricin A protein molecule, however, signals the ER to shut down its UPR and the cell's stress response needed for survival. Ricin becomes activated after proteolytic splitting into A and B components. The ricin A part binds to a specific adenine of 28S ribosomal RNA. It prevents further production of protein in the cell (Buchanan *et al.*, 2004). This toxin is not fat soluble and heating to 140° C destroys the toxin.

Abrin (a toxalbumin protein), a very powerful poison is present in seeds of *Abrus precatorius.* Swallowing just a few of the chewed seeds can be deadly. The plant is commonly known as Ratti or Gunchi in India. The seeds are about 100 times less poisonous when taken by mouth than when injected. Criminals can decorticate the seeds, removing their outer covering. The decorticated seeds are then powdered, mixed with spirit or water and made into a paste. Long thin needles can be formed from this paste and can be dried in the sun. When used to stab a person, enough poison is released to kill the victim.

Gelonin, present in seeds of *Gelonium multiflorum* belongs to the family of single-chain ribosome inactivating proteins (Girbes *et al.*, 2004). It potently inhibits protein synthesis in eukaryotic cells, by cleaving the N-glycosidic bond of a specific adenine in 28S rRNA, which results in the cell death. Gelonin has also been shown to be active on DNA and on other polynucleotides (Barbieri *et al*., 1997; 2000).

Lectins are protein or glycoprotein substances, usually of plant origin, of non-immunoglobulin nature, capable of specific recognition of and reversible binding to, carbohydrate moieties of complex glycoconjugates without altering the covalent structure of any of the recognized glycosyl ligands (Sullivan, 2000). These lectins bind to sugar moieties in cell walls or membranes and thereby change the physiology of the membrane to cause agglutination, mitosis, or other biochemical changes in the cell.

Lectins were first described in 1888 by Stillmark working with castor bean extracts. Many members of the lectinic protein family agglutinate red blood cells. Ehrlich showed that feeding small amounts of lectin containing seeds to rabbits caused partial immunity to the toxicity demonstrating lectins are also antigenic. Lectins from the castor bean are highly toxic and can kill if ingested in even small amounts. Lectins from kidney beans have been implicated as cause in an outbreak of 'food poisoning' with no known pathogen.

Lectins are hardy proteins that do not break down easily. Lectins may bind to the gut wall and damage the gut lining, are not altered by digestive enzymes, and may alter gut permeability and pass through the gut into general circulation. Lectins can cause alterations in gut function that may be related to colitis, Crohn's disease and gut permeability. Lectin damage to the gut wall

may allow other non-lectin proteins to cross undigested into general circulation and cause allergic reactions, including anaphylaxis. Having gained access to general circulation various lectins may bind to surface cell membranes in arteries and vessels, organs and glands, in susceptible animals and humans. This binding may begin antigen-antibody reactions leading to autoimmune disorders and so-called degenerative diseases.

Curare and similar neuromuscular blocking agents are found in several plant types (*Chondrodendron tomentosum* and other genera) and have been used for centuries by Amazonian Indians. The poison is applied to the tips of arrows and death results from paralysis of the pulmonary structures which result in pulmonary failure. Curare blocks nicotinic receptors without stimulation at skeletal neuromuscular junctions resulting in weakness and paralysis. Curare has been used medically to promote muscle relaxation in general anesthesia.

Besides those detailed so far, a large number of plant toxins are known, which may prove of interest with respect to bioterrorism.

Counter Strategies

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. This plan can be relatively effective for the lethal agents listed above 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, 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 designed for bioterror attacks and it can be deployed anywhere across the globe within a short duration 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. With the latest information and advanced expertise to produce resistant variants of biological agents, the terrorist groups could produce bacteria and viruses that can withstand the standard antibiotics and anti-virals used for treatment. 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.

Defense strategies against biological weapons include such measures as enhanced epidemiologic surveillance, vaccination and use of antimicrobial agents, with the important warning that the final line of defense is the immune system of the exposed individual. The potential threat of biological warfare and bioterrorism is inversely proportional to the number of immune persons in the targeted population. Thus, biological agents are potential weapons only against populations with a substantial proportion of susceptible persons. For example, smallpox virus would not be considered a useful biological weapon against a population universally immunized with the vaccine. Vaccination can reduce the susceptibility of a population against specific threats provided that a safe vaccine exists that can induce a protective response. Unfortunately, inducing a protective response by vaccination may take longer than the time between exposure and onset of disease. Moreover, many vaccines require multiple doses to achieve a protective immune response, which would limit their usefulness in an emergency vaccination program to provide rapid prophylaxis after an attack. In fact, not all vaccine recipients mount a protective response, even after receiving the recommended immunization schedule. Persons with impaired immunity are often unable to generate effective response to vaccination, and certain vaccines may be contraindicated for them (Pirofski and Casadevall, 1998). For example, the vaccine against hepatitis B does not elicit an antibody response in approximately 10% of vaccines, and the percentage of non-responders is substantially higher in immuno-compromised persons (Pirofski and Casadevall, 1998). Drugs can provide protection when administered after exposure to certain agents, but none are available against many potential agents of biological warfare. Currently, no small-molecule drugs are available that prevent disease following exposure to preformed toxins. The only currently available intervention that could provide a state of immediate immunity is passive immunization with protective antibody. Passive antibody therapy was widely used in the pre-antibiotic era but was largely abandoned with the advent of antimicrobial chemotherapy (Casadevall and Scharff, 1994; 1995). In recent years, there has been a renaissance in the use of antibodies for therapy: 10 monoclonal antibodies (MAbs) are currently licensed and dozens are in the developmental pipeline (Reichert, 2001). This article reviews the activity of humoral immunity against several biological agents, discusses the advantages and disadvantages of an antibody-based defense strategy, and proposes stockpiling specific antibodies for use in the event of biological attacks (Casadevall, 2002).

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.

Preventive and Treatment Procedures

Antibiotics: The use of antibiotics would be effective only if there was actual exposure, and the biological agent was bacterial and susceptible to the antibiotic chosen for chemo-prophylactic use. In addition, long-term use of antibiotics can have their own problems. The symptoms ranges from individual to individual basis. Common reactions include 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. These are usually reversible on discontinuation of therapy. As a relative safe preventive alternative, especially in the absence of a confirmed exposure, immune enhancers can be recommended (Kabara, 1972; Kabara, 1979; Hierholzer and Kabra, 1982; Enig, 1997).

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 chemo-prophylactic 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 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 (Jones, 1998; Ploegh, 1998; Bernstein 2000; Gulbins and Lang, 2001).

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 (Pomeratnsev et al., 1997; Zajtchtchuk and Bellamy RF, 1997).

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.

Antibody preparations in the form of serum therapy were used historically for the treatment of anthrax (Lucchesi and Gildersleeve, 1941), tularemia (Foshay, 1940), and plague (Strong, 1944)), albeit in uncontrolled trials that do not meet modern standards for establishing efficacy. The major advantage of passive antibody immunization in defense against biological weapons is that it provides a state of immediate immunity that can last for weeks and possibly months. Some human IgG isotypes have serum half-lives in excess of 30 days (Sarvas *et al.*, 1993), which would confer long-lived protection to passively immunized persons. Antibodies are natural products with minimal toxicity, provided that they contain no aggregates and have no reactivity with host tissues. If vaccines are available, simultaneous administration of vaccine and antibody may be possible to provide both immediate and long lasting protection, as is done for rabies in postexposure prophylaxis. Antibodies conjugated to enzymes, radionucleotides, or drugs could provide additional antimicrobial activities apart from those conferred by the native immunoglobulin molecule. Although passive antibody will generally have to be given systemically, oral administration can be useful against certain gastrointestinal agents. With the exception of rabies antiserum, most antibody preparations in clinical use are given intravenously. The need for intravenous administration is a severe constraint for mass passive immunization and would likely limit this practice to a few recipients. However, this disadvantage may potentially be circumvented because Ig preparations can theoretically be administered intramuscularly. Hence, generating antibody preparations suitable for delivery into one of the large muscles of the arm or leg may be possible without the need for logistically complicated intravenous infusions. Such antibody preparations could be supplied in self-injectable devices that could allow susceptible persons to protect themselves upon notification of a biological attack. However, for this scenario to be realistic, antibody preparations with high specific activity would have to be developed that would allow administration in a small volume. An antibody-based defense strategy against biological warfare agents can be supported by a mature technology. Antibody- based therapies were first used in the late 19th century, and more than 100 years of experience has been gained in the development of therapeutic antibodies. In the past, antibody based therapies were dependent on immune serum that was limited in availability and was associated with substantial side effects when the serum originated from

animals (Casadevall and Scharff, 1994; 1995). In recent years, major technical advances in the ability to generate antibodies include the development of a variety of expression systems, including hybridoma, bacteria, and phage systems (Maynard and Georgiou, 2000; Humphreys and Glover, 2001). Since 1997, eight MAbs have been licensed for human therapeutic use; three of these are mouse-human chimerics and five are humanized murine MAbs (Reichert, 2001). Each of these molecules has been the product of advances in biotechnology, and their success supports the view that the technology is in place for implementing an antibody-based defense strategy.

Immunoglobulins are highly versatile effector molecules that can be adapted for use against virtually any infectious agent or toxin. In fact, antibody therapy is now available for a variety of situations in which natural antibody immunity is not likely to be effective, including prevention of re-stenosis after coronary angioplasty and the therapy for venomous animal bites, digitalis toxicity, breast cancer, and Crohn disease (Casadevall, 1999). Furthermore, the fact that natural protection to a given pathogen may rely on cell-mediated immunity does not negate the fact that passive antibody can still mediate protection. For example, protective MAbs have now been identified against such intracellular pathogens as *Ehrlichia chaffeensis* (Winslow *et al.*, 2000), *Cryptococcus neoformans* (Fleurido *et al.*, 1998), *Listeria monocytogenes* (Edelson *et al.*, 1999), *Candida albicans* (Han and Cutler, 1995), and *Mycobacterium tuberculosis* (Teitelbaum *et al*., 1998), for which cell-mediated immunity is critically important for protection.

The availability of antimicrobial therapy does not diminish the advantages of antibody-based therapies. Currently no drugs are available that specifically counteract the activity of preformed toxins, while toxin neutralization is a classical property of antibody-mediated immunity. For certain conditions, antibody therapy may have some advantages over antimicrobial therapy. For example, administration of human IgG may require only a one-time infusion, whereas antimicrobial therapy is likely to require continuous administration during the period of exposure and following infection. Furthermore, bacteria can be relatively easily engineered for resistance to antibiotic drugs. These issues were highlighted during the recent anthrax exposures, when 60 days of therapy was recommended after exposure, with a drug (e.g., ciprofloxacin) that was selected because of concerns about potential resistance in certain strains of *B. anthracis* (Hart and Beeching, 2001). Prolonged use of antimicrobial drugs for prophylaxis against biological warfare agents such as anthrax carries inherent risks of drug toxicity and selection for drug-resistant strains among the host microbial flora (Hart and Beeching, 2001). Antibody defense strategies can be circumvented by the generation of agents that exhibit antigenic variation. MAbs that recognize a critical domain in a microbial antigen are particularly vulnerable to the emergence of antigenic variation arising from selection during person-to-person spread or genetic engineering of the biological agent. Hence,

stockpiles of MAbs an easily be made obsolete by biological agents that exhibit antigenic differences. This problem may be circumvented by using polyclonal antibody preparations or MAb cocktails that bind multiple epitopes in the targeted antigen. The efficacy of antibody preparations can be safeguarded by classifying the binding specificities and characteristics of antibody preparations as state secrets. Furthermore, the possibility of counterstrategies should be incorporated into the design of antibody therapeutics by specifically targeting constant epitopes that are unlikely to retain biological activity if altered. In fact, it may be possible to safeguard the usefulness of antibody preparations designed specifically for protection against biological agents by concealing their specificity in complex preparations that defy immunologic analysis. Currently, we lack sufficient immunologic knowledge to predict the specificities and isotypes that are protective against individual pathogens. Hence, the search for protective antibodies remains empirical. Incidentally, the identification of a protective antibody de facto identifies an antigen that is capable of eliciting a protective antibody response.

Immune Enhancement and Nutrition: Immune enhancement and nutritional approaches are not expected to be full-proof preventive measures that will completely 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.

Conclusion

Bioterrorism is a criminal act of deliberate release of virus, bacteria or other germs and agents to cause illness or death of unsuspecting civilians and

animals or plants. Bioterror agents are dangerous pathogens which most often are colorless, odorless and tasteless microorganisms or toxins (mostly proteins) derived from microorganisms. The agents thus far used for the act of bioterrorism are Anthrax, Plague, Brucellosis, Mycoplasmas, Q fever, Tularemia, Smallpox, Hemorrhagic fever viruses, Botulinum Neurotoxin, Staphylococcal Enterotoxins (SE), Selected Low Molecular Weight (LMW) Toxins and T-2 toxin. Among pathogeni plant proteins which can be potentially used as an agent for bioterrorism are as follows Ricin, Abrin, Gelonin, Lectins and Curare. The counter strategies for these agents are Antibiotics, Antivirals, Vaccines, *Passive Immunization and* Immune Enhancement and Nutrition.

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