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Dilemmas of a Dual-Use Technology: Toxins in Medicine and Warfare

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Abstract. **Several toxins are "dual-use" in that they have legitimate therapeutic, pharmaceutical, or scientific applications as well as potential military utility as toxin warfare (TW) agents. The growing peaceful applications of such toxins may complicate efforts to ban their use for warfare or terrorist purposes. Worldwide consumption of toxins for medical therapy and scientific research has increased from a few grams to the current level of hundreds of grams per year, and the projected future growth of toxin therapies will require tens to hundreds of kilograms of material annually, blurring the distinction between medically useful and militarily significant quantities. As a result, a proliferator might seek to acquire an offensive TW capability under the guise of "peaceful" activities permitted by the Biological and Toxin Weapons Convention (BWC) and the Chemical Weapons Convention (CWC). To examine this problem more closely, the case of ricin—a putative toxin warfare agent with expanding scientific and medical applications—is discussed in detail. Finally, an analysis of policy options for regulating dual-use toxins concludes that precise monitoring of toxin production would be impracticable in many cases, and that international efforts to achieve greater openness and transparency offer the most realistic basis for distinguishing between the legitimate and banned uses of toxins.**

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IN RECENT DECADES, "dual-use" technologies with both commercial and military applications have created a major challenge for arms controllers, who have sought to preserve the economic benefits of these technologies while minimizing their threats to international security. This essential tension is reflected in the elaborate verification and export-control regimes established by the international community to regulate commercial nuclear-power plants and chemical factories that normally engage in legitimate activities but have the potential to be diverted to the illicit production of materials for nuclear and chemical weapons.

Such a dual-use dilemma applies increasingly to the biotechnology sector as well. In recent years, many developing countries have acquired industrial microbiology plants for the production of fermented beverages, vaccines, antibiotics, ethanol fuel (from corn or sugar cane), enzymes, yeast, vitamins, food colorings and flavorings, amino acids, and single-cell protein as a supplement for animal feeds (Office of Technology Assessment, 1991). The global expansion of these industries and the growing number of industrial biotechnologists trained in Western countries have inevitably created broader access to expertise, equipment, and raw materials relevant to the development and production of biological and toxin warfare agents for military or terrorist purposes (Zilinskas, 1990, 1992). Moreover, since biotechnology is information-intensive rather than capital-intensive, much of the required know-how has been published in the scientific literature. For these reasons, it has become virtually impossible to prevent the diffusion of relevant information to states that may wish to develop weapon systems based on pathogens or toxins (Office of Technology Assessment, 1993).

A relatively small number of toxins have both peaceful uses in science and medicine and potential uses as military or terrorist weapons. This article discusses the

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general characteristics of such "dual-use" toxins, examines in detail the case of ricin (a putative toxin warfare agent with expanding medical applications), and concludes with an analysis of policy options for preserving the societal benefits of toxins while managing the risks attendant to their applications.

Toxins as Dual-Use Agents

Toxins are poisonous chemicals manufactured for defensive or predatory purposes by a wide variety of living organisms, including bacteria, fungi, plants, marine organisms, and venomous insects, spiders, reptiles, and amphibians. A few of the natural toxins extracted from plants or animals can also be synthesized chemically in the test tube or produced in bacteria or yeast that have been genetically modified with recombinant-DNA techniques. The extraordinary capacity of toxins to kill or incapacitate at low doses derives from their high specificity for cellular targets. Some toxins bind to specific receptor sites in nerve membranes, disrupting the transmission of nerve impulses and causing fatal respiratory paralysis, while others interfere selectively with cellular protein synthesis or other vital physiological functions.

Types and Characteristics of Toxins

More than four hundred different toxin molecules have so far been characterized. From a biochemical standpoint, there are two broad categories: *protein* toxins, consisting of long, folded chains of amino acids; and *nonprotein* toxins, small molecules that generally have a complex chemical structure including one or more rings of carbon atoms.

Examples of protein toxins are the active ingredients of snake and insect venoms and the bacterial toxins responsible for the symptoms of anthrax, botulism, cholera, diphtheria, staphylococcal food poisoning, and tetanus. For example, botulinum toxin, the causative agent of botulism, is a large protein toxin secreted by the soil bacterium *Clostridium botulinum*. The most poisonous proteinaceous substance yet discovered, it has a potency per unit weight about 10,000 times greater than that of VX, the most deadly nerve agent in the U.S. chemical arsenal (Erlick, 1990). One milligram of botulinum toxin contains enough lethal doses for about 100 people (Harsanyi, 1992).

Nonprotein toxins include tetrodotoxin (produced by a puffer fish), saxitoxin (made by marine microorganisms and concentrated in the tissues of filter-feeding shellfish), microcystin (synthesized by blue-green algae), palytoxin (produced by a soft red Hawaiian coral), and batrachotoxin (manufactured by poison-dart frogs indigenous to South America). Typical characteristics of nonprotein toxins are high toxicity, rapid action, the absence of antidotes, and resistance to heat and other environmental stressors. For example, the lethal dose of saxitoxin in fifty percent of exposed individuals can be as low as fifty millionths of a gram—a potency a thousand times greater than that of VX (Erlick, 1990). Ingestion of a lethal dose results in symptoms of indigestion and dizziness within thirty seconds and causes labored breathing and paralysis in as little as twelve minutes; there is no prophylaxis or effective treatment.

Perhaps the best-known nonprotein toxins are the trichothecene mycotoxins, a family of more than one hundred poisonous compounds elaborated by certain strains of the mold *Fusarium* that grow on grains such as wheat, millet, and barley and may be ingested by people or livestock. A few of these mycotoxins, including T-2 toxin, verrucarin A, and roridin A, can also be absorbed through the skin. Once they enter the body, trichothecene mycotoxins kill the rapidly dividing cells of the bone marrow, skin, and the lining of the gastrointestinal tract; they also interfere with the clotting factors in the blood, resulting in profuse bleeding after injury. Although the trichothecenes are significantly less potent than botulinum toxin or saxitoxin, they are relatively easy to produce and are highly stable.

Peaceful Applications

Toxins have numerous peaceful applications in biomedical research and therapeutics. Hundreds and perhaps thousands of universities, hospitals, and pharmaceutical firms throughout the United States are using toxins as research tools, essential elements in diagnosis and detection, and medical therapies. In addition, at least a dozen companies are developing and marketing drugs based on natural toxins. Botulinum toxin is sold commercially under the tradename BOTOX by Allergan, a biotechnology company in Irvine, California (Ubell, 1993), and under the tradename Dysport by Porton International PLC in the United Kingdom (Harsanyi, 1992). Its primary application is to treat debilitating muscle spasms known as dystonias by selectively paralyzing the abnormal muscles (Waters, 1992). Blepharospasm, for example, a spastic paralysis of eye muscles that leads to functional blindness, afflicts some 5,000 people in the United States each year. It can be treated effectively with injections of botulinum toxin, which inhibits the muscle contraction that keeps the eyes abnormally shut (Heneson, 1991).

The U.S. Food and Drug Administration (FDA) has approved the use of botulinum toxin for the treatment of blepharospasm, strabismus, facial muscle tics, and torticollis (a contracted state of the neck muscles producing an unnatural position of the head), and it is being tested for other disorders such as gastrointestinal spasms (Tucker, 1993). Plastic surgeons have also begun using

botulinum toxin cosmetically to smooth wrinkles (Evangeli, 1993). Other toxins are also finding growing application in medical therapeutics and biomedical research. Ricin, diphtheria toxin, and *Pseudomonas* exotoxin, when linked to monoclonal antibodies that selectively target cancer cells, have shown promise in clinical trials. In addition, saxitoxin, tetrodotoxin, and other exotic toxins bind specifically to ion-channel or receptor proteins embedded in cell membranes and have thus become essential tools in many physiology and pharmacology laboratories.

Military Applications

Toxins might be used for a spectrum of military applications ranging from covert assassination to tactical battlefield use to strategic warfare against population centers. Attacks against human beings might be carried out by four possible routes of exposure: injection, ingestion, inhalation, or—for only a few toxins—absorption through the skin. Since toxins are all nonvolatile solids, however, they could only cause massive casualties if they were delivered as a fine dust or aerosol that remained suspended in the atmosphere for several hours and was inhaled by a large number of people. Only a few toxins have the combination of potency, stability, producibility, and suitability for aerosol dissemination that would allow them to be used as weapons of mass destruction. The most toxic compounds (with a lethal dose less than 0.025 micrograms per kilogram), if delivered through the air as a small-particle aerosol, are theoretically capable of producing massive casualties among unprotected troops. Moreover, some bacterial toxins (e.g., botulinum, staph enterotoxin B) and plant toxins (ricin, abrin) could be produced in sufficient quantities—tens to hundreds of kilograms—to have militarily significant effects.

For tactical military use, toxin warfare (TW) agents would offer at least four advantages over microbial pathogens. First, toxins act much more rapidly than infectious agents, exerting their incapacitating or lethal effects in several minutes to hours rather than in days. They are also more controllable and self-limiting since they do not reproduce or spread from one individual to another. Second, the extraordinary potency of the most deadly classes of toxins—nearly all of which are bacterial in origin—means that relatively small quantities of agent, if disseminated efficiently through the air, could cause casualties over a wide area. Third, since most toxins deteriorate rapidly after release into the environment, territory attacked with toxin agents could be occupied more rapidly by invading forces. In contrast, anthrax spores and persistent chemical warfare (CW) agents can contaminate soil for months or years, making it equally hazardous to attacking and defending troops. Fourth, toxins are well-suited for covert warfare or economic sabotage because their use can be difficult to detect, let alone prove. Whereas the breakdown of CW agents results in telltale degradation products that can persist in the environment for as long as a few years, toxins break down completely over a period of weeks or months, leaving no traces that can be identified using currently available technologies. Moreover, even fresh samples of toxin might not provide conclusive evidence of military use if the agent occurred naturally in the area where it was employed.

As their availability increases and production costs fall, toxins may become more attractive for low-intensity warfare and special-forces operations, as well as terrorism

Partially offsetting these military advantages of toxins, however, are a number of serious drawbacks. Without a massive research and development effort, problems of weaponization and delivery will continue to limit the practicality of toxins for large-scale, open-air dissemination. Many protein toxins, such as botulinum, decompose rapidly on exposure to sunlight and hence could probably only be used at night, or in conjunction with stabilizers that would dilute their potency. Protein toxins may also be inactivated by heat, air pollution, or the mechanical shear forces associated with passage through an aerosol sprayer. In general, nonprotein toxins such as saxitoxin and the trichothecene mycotoxins are more stable than protein toxins but less stable than man-made CW agents.

Furthermore, unlike persistent CW agents such as sulfur mustard or VX, most toxins—with the exception of a few trichothecene mycotoxins—are incapable of penetrating the skin. They are also nonvolatile solids and thus pose a respiratory threat only if disseminated as a suspended aerosol of microscopic particles; unlike persistent CW agents, toxin lying on the ground would not create a vapor hazard (Freeman, 1990). Finally, the inhalation threat posed by protein toxins such as botulinum can be countered effectively with modern gas masks, although—as is the case with chemical agents—a surprise or covert attack might expose personnel to lethal concentrations of agent before they had time to don their masks. In sum, for conventional battlefield use, toxins appear to offer few military advantages over existing CW agents. As their availability increases and production costs fall, however, toxins may become more attractive for low-intensity warfare and special-forces operations (e.g., behind-the-lines attacks against enemy command-control centers), as well as terrorism.

Although ricin and saxitoxin have both been developed as assassination weapons (the former by the Soviet KGB and the latter by the U.S. Central Intelligence Agency, as revealed during a Senate investigation headed by Senator Frank Church), there has been only one case of alleged toxin warfare. In 1982, the Reagan Administration accused the Soviets and their Vietnamese allies of attacking the H'mong tribesmen of Laos and Cambodia with a lethal agent termed "yellow rain," whose active ingredients were claimed to be trichothecene mycotoxins (U.S. Department of State, 1982). The Soviets denied the allegation, and the U.S. Government was unable to provide convincing public evidence to back up its charges in the face of skepticism from the international scientific community (Robinson et al., 1990; U.S. Senate, 1993). Although U.S. intelligence officials have not retracted their yellow-rain assertions, most of the relevant information remains classified, making it impossible to assess their claims in the open literature. During the 1991 Persian Gulf War, Iraq was assessed to have developed botulinum toxin as a TW agent and to have produced it in militarily significant quantities (U.S. Dept. of Defense, 1992). Nevertheless, there is no available evidence that Iraq was able to weaponize botulinum toxin for dissemination with available delivery systems, and it is extremely unlikely that biological or toxin weapons were used during the conflict.

Acquisition of Toxin Weapons

In order to develop effective policies for the control of toxin weapons, it is useful to understand how toxins might be developed and mass-produced for this purpose. States or terrorist organizations seeking a toxin warfare capability would probably start with the development of standard agents that have been weaponized in the past, such as botulinum toxin. These agents might be obtained from biological supply houses, which ship vials of purified toxins and strains of toxin-producing bacteria to scientists and public-health researchers throughout the world. Alternatively, potent toxins could be derived from natural sources such as soil bacteria, diseased animals, poisonous plants, and animal venoms. Methods for culturing microorganisms and extracting toxins from plant and animal tissues are described in detail in the scientific literature.

Some countries of proliferation concern may eventually attempt to apply the new biotechnologies to develop "improved" TW agents with greater military utility (External Affairs and International Trade Canada, 1991). Most developing countries still lack access to sophisticated genetic-engineering techniques such as recombinant-DNA technology, but these methods are gradually diffusing throughout the world with the expansion of the commercial biotechnology industry (Tucker, 1984). Although it is unlikely that synthetic toxins could be developed that would be significantly more deadly than those that already exist in nature, genetic engineering might be applied to

1. alter the antigenic structure of toxin molecules, reducing the ability of a defender to detect them with antibody-based techniques or to neutralize them with existing antitoxins;
2. combine two different toxin molecules, such as ricin and diphtheria toxin, into a hybrid or "chimeric" toxin that is more capable of penetrating and killing target cells;
3. increase the stability of toxins in the environment, enabling them to remain effective for a longer period after being disseminated as a suspended aerosol;
4. increase the potency of protein toxins per unit weight by removing those portions of the toxin molecule that are not essential for its physiological action; and
5. design analogs of existing toxins, perhaps consisting of little more than the biologically active region of a protein toxin. Such peptides might be as potent as chemical nerve agents, yet small enough to penetrate the filters used in gas masks and protective garments.

Modifications 1 and 2 could be accomplished with technologies available today (Ready, Kim, and Robertus, 1991); numbers 3 and 4 appear feasible within five years; and number 5 might be possible within a decade.

Once a nation seeking a TW capability had acquired potential toxin agents, several additional steps would be required to turn them into weapons with reasonably predictable effects. First, the toxins would have to be assessed for their military effectiveness, which would depend upon level of toxicity, the effective dose, environmental stability, feasibility of aerosol dissemination, and delivery mechanisms. This process of advanced development and weaponization would also require extensive testing, which might be carried out either inside a sealed aerosol test chamber or at a remote outdoor testing range. If tests involving toxin aerosols were detected, they would be a strong indicator of offensive military intent—although the country involved would probably describe such activities as defensive.

Toxins could be manufactured in militarily significant quantities with both low-tech and high-tech methods. Bacterial toxins such as botulinum, for example, can be produced in glass flasks, although efficient large-scale production requires the use of a fermenter that precisely regulates the culture conditions. If *Clostridium botulinum* bacteria are grown at the right temperature and acidity and in the absence of oxygen, it takes only about three days for them to multiply into a dense suspension of cells, which extrude toxin into the surrounding culture medium. Although highly pure toxin is required for medical and research applications, purification is

neither necessary nor desirable for weaponization because it is costly, results in a considerable loss of material, and tends to reduce stability. Instead, relatively simple extraction methods could provide crude toxin adequate for use as a weapon.

Animal toxins are much harder than bacterial or plant toxins to produce in militarily significant quantities. Even small amounts of such toxins must be extracted from large quantities of feed material with costly and labor-intensive purification techniques. For example, less than 5 grams of saxitoxin were purified from 270 kilograms of toxin-contaminated clam siphons (Schantz et al., 1957). Although saxitoxin can be chemically synthesized in a multi-step process, the overall yield is only 0.1 percent, making it unlikely that militarily significant quantities could be produced by this method (Sanches et al., 1991)

Using recombinant-DNA techniques, however, molecular biologists can genetically program microbes to manufacture certain animal toxins in kilogram quantities (Tucker, 1992). Although such methods are now restricted mainly to the advanced industrial countries, they are diffusing rapidly into the developing world. One approach, known as "cloning" of toxin genes, involves identifying the DNA sequences that encode for protein toxins, isolating and transferring the DNA strands to a suitable microbial host, and culturing the toxin-producing microbes in a fermenter. In this way, ordinary bacterial or yeast cells can be transformed into miniature toxin factories (Wiseman, 1992). In some cases, however, the expression of plant or animal toxin genes in bacteria would have to overcome certain technical hurdles. Bacteria typically produce and secrete toxins only under special conditions that may not be met in an artificial environment. Furthermore, bacteria may be unable to perform certain key biochemical processing steps, such as the addition of sugar molecules needed to convert some protein toxins to their biologically active form (Novick and Shulman, 1990). Mass-production of non-protein animal toxins in bacteria is theoretically possible, but the technical hurdles would be even greater. In such cases, it would be necessary to clone a "cassette" of genes coding for an entire series of enzymes, each of which would be needed to catalyze one step in the toxin's biosynthetic pathway (Primrose, 1991).

After a crude preparation of toxin had been produced through fermentation or extraction, it could be converted into a solid cake by rapid freezing and dehydration under a high vacuum, a process known as freeze-drying or "lyophilization." The cake of freeze-dried toxin could then be milled into a fine powder or dust—an exceedingly hazardous operation that would have to be carried out under conditions of high containment. Toxin dust disseminated as an aerosol would be deadly in extremely small quantities. In one study, saxitoxin and T-2 mycotoxin proved at least ten times more toxic in aerosol application than in intravenous injection (Government of the USSR, 1991). For effective airborne dissemination, however, the toxin particles would have to be 1 to 5 microns (thousandths of a millimeter) in diameter. Only particles with those dimensions are retained deep in the lungs; particles smaller than 1 micron are reexhaled, while those larger than 5 microns are trapped in the respiratory passages.

Lyophilization also improves the stability of many toxins, extending their shelf-life to a period of several months. A second approach to toxin stabilization, known as "microencapsulation," involves coating microscopic particles of toxin with a thin coat of gelatin, sodium alginate, cellulose, or some other protective material. Microencapsulation can be performed with physical or chemical methods (Osol et al., 1975). A similar technique is used to make carbonless carbon paper, in which microscopic ink droplets are coated with a polymer. The microcapsule would protect the toxin molecules against desiccation, prolong their stability in the atmosphere, and make otherwise extremely hazardous agents safer to handle. Microcapsules could also be charged electrostatically to reduce particle clumping during dissemination, and ultraviolet-blocking pigments could be added to the capsule material to shield the toxin against degradation by sunlight (Government of Australia, 1991). In principle, once microencapsulated particles of toxin had lodged deep inside the lung, the polymer coating would dissolve, releasing the active agent. Nevertheless, the microencapsulation of toxins remains an unproven technique and could well be complicated by technical problems, such as the reduced stability of microencapsulated toxins, the generation of particles too large to lodge in the lung, or the failure of the capsules to dissolve and release the active agent.

Delivery systems for TW agents could range in complexity from modified crop-spraying equipment mounted on a truck or aircraft to a specialized cluster warhead carried on a ballistic or cruise missile. The difficulty of delivery-system development would depend on the military objective. It would not be particularly difficult to spread an aerosol cloud of toxin agent in an indiscriminate manner for the purpose of producing large numbers of casualties over a wide area. Depending on the vagaries of the wind and weather, an airborne agricultural spray-tank containing a suspension of botulinum toxin might expose tens of thousands of people to a lethal dose of agent, but this means of delivery would not be particularly controllable or predictable (for example, it might backfire against the attackers if the tank leaked or the wind shifted unexpectedly). A technically more difficult task would be to develop toxin-carrying munitions that have predictable or controllable military effects against small-area targets such as troop concentrations on the battlefield. During the 1960s,

The amount of toxin needed to pose a significant military or terrorist threat is not much greater than the quantities now being produced for legitimate biomedical research and medical therapy

however, both the United States and the Soviet Union appear to have developed effective munitions for the delivery of a few biological and toxin agents.

International Law Controlling Toxin Warfare

Because toxins are nonliving compounds made by living organisms, they exist in a gray area between man-made chemical warfare agents and biological warfare agents. Toxins are covered under international law by both the Biological Weapons Convention (BWC), which entered into force in 1975, and the Chemical Weapons Convention (CWC), which is expected to enter into force in 1995 (Conference on Disarmament, 1993). The BWC bans the production of both natural and synthetic toxins "in types and in quantities that cannot be justified for prophylactic, protective and other peaceful purposes" (Conference on Disarmament, 1972). However, it does not explicitly limit the quantities of toxins that may be produced for legitimate purposes, nor does it include formal mechanisms for the verification and enforcement of compliance.

Like the BWC, the CWC bans the development, production, acquisition, stockpiling, transfer, and use of all toxic chemicals for offensive military purposes, while permitting development and production of dual-use chemicals on a limited scale for "nonprohibited" (i.e., peaceful or defensive) purposes. The CWC also establishes a formal verification regime that imposes declaration and on-site inspection requirements on production (and in some cases, processing and consumption) of a variety of toxic chemicals and precursors, which are listed on three "schedules" of chemicals in an annex to the treaty. Nevertheless, the CWC verification regime covers the production of only two natural toxins, saxitoxin and ricin. During the CWC negotiations in Geneva, the decision to include these particular toxins in the verification regime was somewhat arbitrary, and was intended as a "placeholder" that could be modified or expanded in the future.

The CWC's Annex on Chemicals places saxitoxin and ricin on a list called "Schedule 1," which includes all known chemical-warfare agents and their final-stage precursors (Conference on Disarmament, 1992). Once the CWC comes into force, production of Schedule 1 chemicals will be regulated along the following lines:

- At any given time, a State Party may not possess more than a total of 1 metric ton of all Schedule 1 chemicals, including saxitoxin and ricin, for nonprohibited activities.
- Within the 1 metric ton aggregate limit, the production of a Schedule 1 chemical for legitimate medical, pharmaceutical, or research purposes is limited to a maximum of 10 kilograms per year at any facility.
- Any government-owned or private facility that produces more than 100 grams per year of a Schedule 1 chemical must file an initial declaration, to be followed by annual reports updating its activities.
- All declared Schedule 1 production facilities are subject to systematic on-site inspections.

In sum, both the BWC and the CWC allow the production and use of toxins for peaceful purposes and the development of chemical and biological defenses (e.g., vaccines, antidotes, and protective garments). In the case of dual-use toxins, however, this exemption is associated with two dilemmas. The first is that up to the point of weaponization, the development of toxins for warfare purposes is largely indistinguishable from their acquisition for legitimate biomedical applications. Assessing compliance with the BWC therefore relies on an assessment of "intent"—a subjective judgement for which no precise criteria exist. For example, before and during the 1991 Persian Gulf War, the United States manufactured large quantities of botulinum vaccine (toxoid) to immunize thousands of U.S. troops against botulinum toxin, which the Iraqis were believed to have stockpiled for warfare purposes (U.S. Department of Defense, 1992). Production of the protective toxoid first required the cultivation of large quantities of botulinum toxin, which was treated with formalin to inactivate it while preserving its immunogenic properties. Until the toxin was actually inactivated, however, there was no objective way of knowing whether it was being produced for illicit offensive use or for legitimate defensive purposes.

A second dilemma associated with dual-use toxins is that the amount of toxin needed to pose a significant military or terrorist threat is not much greater than the quantities now being produced for legitimate biomedical research and medical therapy. Over the past few decades, the consumption of toxins for medical therapies, pharmaceuticals, and biomedical research has increased from a few grams per year to the current level of hundreds of grams per year. By the year 2000, annual consumption of toxins for legitimate purposes is projected to rise into the hundreds of kilograms (Zelicoff, 1993). Thus, the anticipated future growth in the biomedical applications of toxins will eventually blur the distinction between legitimate and militarily relevant quantities.

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Harsanyi (1992) contends that control over the legitimate medical uses of toxins is not a problem because physicians employ such agents in minute amounts. For example, since the therapeutic dose of botulinum is 1,000 times less than the lethal dose, anyone ordering a thousand vials of toxin to treat a muscle spasm would be sure to arouse suspicion. The real concern, he contends, is not with pharmaceutical production of highly pure toxin but rather with clandestine facilities that manufacture crude toxin for military use.

As the utilization of certain toxins for biomedical purposes expands over the next decade, economic interests such as the pharmaceutical industry will lobby for looser controls on the manufacture of dual-use toxins. Indeed, botulinum toxin, known to have been developed in the past as a toxin warfare agent, was excluded from the CWC verification regime because its already extensive medical and scientific uses made stringent controls appear impractical. As ter Haar (1991) has pointed out, however, there is a direct rather than inverse relationship between the extent of a toxin's civilian uses and the risk it poses to the disarmament regime. As larger quantities of dual-use toxins become more available, the danger that they might be misused for military or terrorist purposes will inevitably increase as well. This heightened risk would argue for strengthening rather than weakening the controls on such materials.

Ricin as a Case Study

In an effort to clarify some of the issues raised above, the following case study focuses on ricin, a protein toxin of plant origin that has both therapeutic and potential military applications. Ricin illustrates many of the dilemmas of dual-use toxins: it has growing applications in medical therapeutics, yet in recognition of its military potential it is subject to stringent verification requirements under the CWC.

Although ricin is not as potent as botulinum toxin, it is nevertheless a lethal poison. The fatal dose for the mouse, rat, and dog is about 1 microgram of toxin per kilogram of body weight (Fodstad et al., 1979). Respiratory exposure to ricin is even more deadly than intravenous injection: a single inhalation of ricin dust produces severe diffuse necrosis of the respiratory tract tissue (Wannemacher et al., 1990), and inhaled ricin is 8 to 10 times more toxic than the chemical nerve agent sarin on a weight-to-weight basis (Cookson and Nottingham, 1969). Purified ricin is odorless, colorless, and fairly stable, retaining its activity even when heated up to 50 degrees Celsius. Although ricin deteriorates slowly at room temperature, it can be stored for two to three months at 4 degrees Celsius (Wannemacher et al., 1990).

Ricin is a large protein consisting of two nonidentical polypeptide chains, designated A and B, which are chemically linked (Robertus, 1989). The function of the B-chain is to recognize and bind to sugar molecules on the surface of living cells, after which the toxin-sugar complexes are drawn into the cell interior. Once inside the cell, the A-chain is released from the complex and becomes active, specifically attacking ribosomes, the submicroscopic cellular particles that orchestrate protein synthesis (Olsnes, 1977).

The mechanism of action of the ricin A-chain is to catalyze a reaction that modifies the chemical structure of the ribosome at one site. This modest chemical change is sufficient to inactivate the ribosome irreversibly, rendering it incapable of coordinating protein synthesis. (Ricin blocks protein synthesis in mammalian cells but not in bacterial cells, which contain a structurally different type of ribosome.) Because the ricin A-chain functions like an enzyme, it can repeat the ribosome-deactivating reaction many times, ultimately shutting down all protein synthesis and leading to the death of the cell. Indeed, a single ricin A-chain has been shown to inactivate about 1,500 ribosomes per minute in a simple buffer solution (Olsnes and Pihl, 1982). This remarkable catalytic activity accounts for the high potency of ricin as a poison.

Ricin is relatively easy to extract from the beans of the castor plant *Ricinus communis*, which is cultivated commercially in many parts of the world for the production of castor oil. The plant is prolific and easy to grow in both temperate and tropical climates. There is no prohibition against cultivating castor, and the seeds can be ordered from several commercial catalogues. Although castor oil is best known as a powerful laxative whose bitter taste caused it to be "dreaded by children since the time of the early Egyptians," its medicinal use has declined sharply in recent decades and is currently of little importance (Gilman, 1990). Nevertheless, castor oil has numerous industrial applications in the manufacture of paint resins, varnishes, nylon-type synthetic polymers, cosmetics, and insecticides, as well as in the textile dyeing and the leather industry (Atsmon, 1989). Hydrogenated castor oil is also used as a lubricating grease (Mariwala, 1993). The leading producers of castor beans are India, Brazil, the former Soviet Union, China, and Thailand. World production has been stable for the last 20 years at about 1 million metric tons per year, despite sharp fluctuations in certain countries (Atsmon, 1989).

Castor oil comprises about 55 percent of the shelled beans and can be extracted by mechanical pressing or chemical processing. After the oil has been removed from the seeds, the residue or "mash" contains about 5 percent ricin by weight (Balint, 1974). This material is normally steam-heated to inactivate the toxin; it can then be used as a fertilizer or animal feed. If the intent is to purify ricin, however, the inactivation step is omitted; it can then be purified from the mash in a two- or three-step biochemical process involving ammonium-sulfate

fractionation, affinity chromatography, gel filtration, or ion-exchange chromatography (Lin and Li, 1980; Simmons and Russell, 1985). Yields of purified ricin are high, typically in the range of 1 gram of toxin per kilogram of seeds. For this reason, there is little incentive to produce ricin synthetically, although it can be produced in bacteria that have been genetically modified by recombinant-DNA methods (Robertus et al., 1987).

Ricin as a Therapeutic Agent

A century ago, after observing the specificity of antigen-antibody interactions, the German immunologist Paul Ehrlich conceived of the idea of "magic bullets"—drugs that would specifically attack diseased cells while sparing healthy ones. Yet it was not until the advent of monoclonal antibodies (identical antibodies produced by a single immortalized line of cultured lymphocytes) that it became possible to develop such targeted therapeutic agents. Several laboratories are currently developing hybrid molecules consisting of a ricin A-chain bound to a monoclonal antibody specific for the unique proteins (tumor antigens) on the surface of cancer cells. After being injected into the bloodstream, the antibodies attach to the targeted cells, which are then selectively killed by the toxin molecules.

To make antibody-toxin conjugates, or "immunotoxins," scientists first remove or inactivate the ricin B-chains that normally bind to many cell types, causing indiscriminate toxicity. The B-chains are then replaced with monoclonal antibodies specific to cancer cells (Thorpe and Ross, 1982). This is done either by joining the toxic A-chain to the antibody with a chemical cross-linker, or by splicing together the genes coding for the A-chain and the antibody and producing the recombinant protein in bacteria (FitzGerald and Pastan, 1989). Since ricin and conventional anticancer drugs have different mechanisms of action, they may have complementary therapeutic effects. Moreover, immunotoxins are minimally harmful to healthy tissues: if the antibody-toxin complexes break down and the A-chains are released into the bloodstream, they do not damage healthy cells because they cannot exert their toxic effects without binding to specific target proteins on the cell surface (Olsnes and Pihl, 1982).

Initially, oncologists hoped that immunotoxins would be curative for both solid tumors and leukemias, but preliminary clinical trials suggest that this approach may be most effective as a supplement to existing therapies. Traditional chemotherapy is more effective at reducing the bulk of tumor cells, while immunotoxin therapy may be better at eliminating residual cells (FitzGerald and Pastan, 1989). The effectiveness of immunotoxin therapy has also been limited by a number of technical problems. First, the body rapidly produces neutralizing antibodies to both the toxin and the antibody, limiting the effectiveness of the treatment to about two weeks. Second, the large size of the toxin-antibody complexes may prevent them from penetrating deep inside a solid tumor to reach all of the diseased cells. Third, only a small fraction of the ricin A-chains actually migrate from the cell surface to the interior of a given cell to exert their lethal effects. One assessment concludes that all these problems are potentially soluble, however, and predicts "the definition of a clear therapeutic role for immunotoxins before the turn of the century" (Hertler and Frankel, 1989).

Ricin has other promising medical applications as well. Immunotoxins incorporating ricin have been used in bone-marrow transplantation to purge leukemic or immunologically active cells from harvested marrow before infusing it into a genetically nonidentical host (Vitteta and Uhr, 1984). Ophthalmologists at Baylor University in Houston have used ricin-conjugated antibodies to inhibit the proliferation of cells that cause secondary cataracts (Harsanyi, 1992). And neuroscientists have used ricin to make anatomically selective lesions in peripheral nerve cells for anatomical mapping and neurophysiological studies (Wiley and Oeltmann, 1991).

Biotechnology and pharmaceutical companies in the United States and Europe are currently developing new drugs based on ricin immunotoxins. A leader in this field is ImmunoGen (Cambridge, Massachusetts), which is engaged in Phase III clinical trials of ricin conjugates for the treatment of chronic lymphocytic leukemia and B-cell lymphoma, a common affliction of AIDS patients. Company scientists learned that the ricin B-chain is not only responsible for binding to cell-surface receptors, but also promotes the translocation of the two-chain toxin across the membrane and into the cell interior. Thus, instead of removing the B-chain, the scientists chemically blocked its binding sites and conjugated the two-chain toxin with a monoclonal antibody specific to cancer cells. This approach significantly improved the toxin's ability to kill tumor cells and hence its therapeutic effectiveness. Pending approval by the FDA, ImmunoGen plans to market its ricin immunotoxin in mid- to late 1996 (Taylor, 1993).

ImmunoGen buys purified ricin from Inland Laboratories (Austin, Texas) and then modifies and conjugates the toxin with monoclonal antibodies. Current consumption of ricin for clinical trials is small (about 1 kilogram per year), but if the FDA approves the drug for manufacturing, annual production could reach into the tens of kilograms for cancer treatment alone. ImmunoGen is also planning other therapeutic applications of ricin immunotoxins that could significantly exceed this production level. The company projects that by the year 2000, worldwide commercialization of the four ricin-based products now in clinical development will require the use of between 50 and 100 kilograms of the toxin per year, clearly overlapping with amounts considered

militarily significant (Taylor, 1993). The impending large-scale production of toxins for legitimate purposes therefore increases the urgency of strengthening the international regime banning their military use.

Ricin as a Potential Weapon

During World War II, the United States, Canada, Britain, France, and Japan investigated ricin as a candidate warfare agent because of its high toxicity and insidious action. A U.S. pilot production plant extracted a total of about 1,700 kilograms of ricin from castor beans for development purposes. Meanwhile, the British developed and tested an experimental ricin weapon known as the "W bomb," a 500-pound cluster unit containing four-pound bomblets filled with the freeze-dried toxin (SIPRI, 1971). The Japanese, for their part, tested the effects of ricin on human subjects by adding it to the food of prisoners of war (Murphy et al., 1984). Despite these exploratory activities, however, ricin was never used in combat.

After World War II, U.S. military interest in ricin continued, and the Army filed a patent for its production process in July 1952. The Soviet Union and its Warsaw Pact allies, particularly Hungary and Czechoslovakia, also did extensive military research on ricin during the Cold War (Harris and Paxman, 1982). Even so, the only documented hostile use of ricin has been as a covert assassination weapon (Knight, 1979). In September 1978, Georgi Markov, a Bulgarian dissident living in London, was walking near the Thames River when a stranger jabbed him in the back of his right thigh with an umbrella tip. After a few hours, Markov developed a high fever; he died of heart failure two days later. When forensic scientists from Scotland Yard examined his body, they discovered a metal sphere the size of an air-gun pellet embedded beneath the skin of his thigh. The pellet had small indentations that appeared to have contained a poison, but it could not be identified. Presumably the pellet had been injected under Markov's skin by a compressed-air gun concealed inside the stranger's umbrella.

A similar but botched assassination attempt that had occurred ten days earlier in Paris provided a solution to the mystery. Vladimir Kostov, another Bulgarian dissident living in exile, had been riding on the Paris Metro when he felt a sharp pain in his back. He subsequently developed a high fever but recovered after a few days. On learning of Markov's death, Kostov requested a thorough medical exam. X-rays of his back revealed a pellet embedded under the skin. The pellet was surgically removed and chemical analysis revealed that it still contained traces of ricin; the wax sealing the indentations in the pellet had not melted completely, preventing the full release of the toxin into the victim's bloodstream (Harris and Paxman, 1982). Suspicion for both assaults fell on the KGB-trained Bulgarian secret police, which sought to silence all criticism of the regime of President Todor Zhivkov. Former KGB General Oleg Kalugin later admitted that he had dispatched an assistant to Sofia to advise the Bulgarian authorities on the assassination campaign, and that the KGB had provided the umbrella-gun and the ricin-containing pellets (Wise, 1992).

Ricin appears to be of considerable interest as a toxin warfare agent among certain states believed to be acquiring biological weapons, particularly in the Middle East. They are interested because ricin, which is considerably more lethal when inhaled than when injected, could be disseminated as a particulate aerosol to kill large numbers of troops or other personnel over a wide area. According to a published report citing U.S. intelligence sources, Iran imported 120 metric tons of castor beans, from which ricin was extracted in pharmaceutical plants (Waller, 1992). Assuming a rough yield of 1 gram of ricin per kilogram of castor beans, Iran could have purified from that one shipment as much as 120 kilograms of toxin—a militarily significant quantity.

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Conclusions and Policy Options

The ricin case study suggests that the dual-use nature of certain toxins makes the selective control of militarily-relevant activities extremely difficult. Indeed, according to a pessimistic assessment, "Since it is impossible to negotiate an end to scientific research and technological endeavor in the field of pharmacology and medicine, it is equally impossible to limit possibilities for malicious misuse of the same research" (Hansen, 1990:55). In an attempt to find some solution to what is clearly a difficult problem, however, three possible options are discussed below.

Option I: Intensive Monitoring

Since relatively small quantities of certain dual-use toxins could be militarily significant, monitoring the production of such toxins to an adequate level of confidence under the CWC (or the BWC, if a compliance-monitoring regime is eventually negotiated) would require a high

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degree of intrusiveness. It would be difficult and costly to inspect all declared production sites with sufficient frequency and intensity to rule out illicit toxin production, and undeclared sites could probably engage in clandestine production without being detected. Indeed, for the most lethal toxins such as botulinum, it would be possible for a manufacturer to underreport or to divert a portion of production over a period of months or years, thereby accumulating a sizeable clandestine stockpile.

Although ricin is significantly less potent than botulinum, it is generated as a byproduct of castor-oil extraction in such large quantities that a strict accounting of its production with "mass-balance" techniques (which compare production inputs and outputs to detect the diversion of sensitive materials) would not be practicable. Indeed, the amount of pure ricin produced for legitimate purposes represents such a tiny fraction of the many tons of ricin-containing mash generated in the production of castor oil that it would tend to get lost in the statistical "noise." A further complicating factor is the sheer number of castor bean-processing facilities in the developing world. According to the president of the Indian Chemical Manufacturers Association, "In India, there's a castor-crushing plant almost on every street. It's practically a cottage industry" (Mariwala, 1993). For this reason, it would be easy for a small-scale producer to neglect to inactivate the mash derived from the production of castor oil, and to use or sell this material for the illicit extraction of toxin. There would be no reasonable hope of detecting that the mash had not been inactivated or of tracking the extracted ricin to its ultimate destination.

Another problem is that there is no standardized detection method or assay for ricin. Detection of toxins at a distance (e.g., with air-sampling techniques) is generally not feasible because they are solids at room temperature and hence lack volatility. Environmental sampling is also problematic since ricin decomposes quickly and leaves no detectable residue, so that it would have to be detected shortly after it had been released. All these practical difficulties suggest that an intensive monitoring regime designed to prevent the diversion of dual-use toxins for military purposes would be costly and not particularly effective. Nevertheless, systematic inspections of declared toxin-producing facilities, such as pharmaceutical and vaccine plants, may have some useful deterrent effect by increasing the risk of using commercial facilities for illicit toxin production and thereby raising the economic and political costs of noncompliance. Verification measures would only apply to countries that have signed and ratified the CWC.

Option II: Openness and Transparency

An alternative to intensively monitoring the production of dual-use toxins would be to promote openness and transparency with respect to their legitimate applications through annual declarations and data-exchanges, thereby building confidence that these materials are not being employed for illicit purposes. For example, at research or industrial facilities that utilize toxins, one might look for discrepancies between the facility's declared activities and its actual output, be it intellectual (e.g., published papers) or industrial (e.g., vials of pharmaceuticals). If the output is not consistent with the organization's declared purpose, there would be grounds for suspicion. Transparency and mutual confidence might also be enhanced by arranging scientific collaborations and exchanges among countries engaged in toxin-related research for peaceful purposes. Such a program might be organized along the lines of a recent proposal for the collaborative development of vaccines against dual-use microbial pathogens (Geissler, 1992). In addition, the civilian scientific community should be educated about the problem of dual-use toxins so that researchers who become aware of illicit activities can play a "whistleblowing" role.

Option III: Early Detection of Illicit Use

Countries engaged in the clandestine development and production of biological and toxin warfare agents are unlikely to participate voluntarily in the transparency measures suggested in Option II. For this reason, some type of system designed to detect the possible use of toxin weapons should be established as a last resort. Several epidemiologists have proposed the creation of an international network of research centers to monitor the emergence and spread of new epidemics, linked to a global rapid-response system (Henderson, 1992). Beyond its obvious public-health benefits, such a global surveillance mechanism would make it easier to distinguish artificially-induced epidemics associated with the covert use of biological warfare agents from natural outbreaks of disease (Wheelis, 1992). This proposal should be expanded, however, to cover significant outbreaks of toxin poisoning. Such outbreaks might be of natural origin, the result of an accidental release of toxins from a civilian or military production facility, or the consequence of deliberate military or terrorist use. The ability of a surveillance network to detect any significant employment of toxin weapons by "rogue" states might help to deter such use, since the attacker would have reason to fear the political and military consequences of exposure.

In sum, although the intensive monitoring of toxin production would help to strengthen the TW disarmament regime, increased transparency with respect to research, development, production, and consumption of dual-use toxins appears to be the most realistic option for managing the problem—to the extent that nation-states are willing to cooperate in this area. As a backup measure, a global epidemiological surveillance network

that tracks outbreaks of toxin poisoning might help deter rogue states from resorting to covert toxin warfare, and it would also reinforce the global norm against the acquisition and use of toxin weapons. Strengthening this norm—which appears linked to an instinctual human revulsion toward poisons—offers perhaps the best hope for controlling the "dark side" of dual-use toxins, while preserving their significant health and scientific benefits.

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