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Ricin: A Possible, Noninfectious Biological Weapon

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1. INTRODUCTION

On September 7, 1978, 49-year-old Bulgarian exile named Georgi Markov was hit by an umbrella's tip while waiting in a bus station in London. The next day, he was admitted to a hospital in a severe condition, which rapidly deteriorated, terminating in his death 4 days later. A tiny pellet was removed from his thigh in autopsy. Based on the clinical course and on the pellet dimensions, it was concluded that Markov was assassinated using the poison ricin (Crompton and Gall, 1980; Franz and Jaax, 1997).

This unique event raised the interest in ricin as a biological weapon. Being known for centuries as a phytotoxin produced from Castor beans, ricin was developed in modern times as a weapon in between the two world wars and later on. Ricin, suspected of being produced as a biological weapon, was found in London and in Paris as recently as 2003 (Koppel *et al*., 2003; Mayor, 2003). Its plant origin makes ricin available and easy to produce – thus attractive to terrorist groups and perhaps to rogue countries. In this chapter, we will review various aspects of ricin as a biological weapon.

2. HISTORY

The castor beans are known for their high toxicity for centuries. In ancient times, farmers knew to keep their livestock away from the castor plant or else they would risk loosing them. The seeds have been also used in folk medicine against a wide variety of diseases (Franz and Jaax, 1997). The castor bean plant *Ricinus communis* originated from Asia and Africa, but today it can be found also in Europe and America (Olsnes and Pihl,

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1976). It is assumed that the kikaion mentioned in the Bible is a variant of the plant (*Old Testament*, 1982). The castor beans are commonly used as ornamental beans, prayer beads, bracelets, or necklaces. They have an outer shell that must be broken to cause toxicity (Hostetler, 2003). Castor oil – an extract of the castor bean plant – has been used for a number of purposes in ancient Egypt.

Stilmark, in the late 19th century, was the first to obtain evidence that the toxicity of the castor bean refers to a toxic protein he named ricin. In his extensive research, he observed that the toxin causes agglutination of erythrocytes and precipitation of serum proteins (Olsnes and Pihl, 1976).

The ricin toxin was first developed as weaponry by the United States, Canada, and the UK during and in between the two world wars. The U.S. army named it: "compound W." Hundreds of kilograms were produced and armed into bombs, which were never used (Franz and Jaax, 1997). Ricin's production and research for offensive use is prohibited according to the Biological and Toxin Weapons Convention from 1972. Ricin, along with saxitoxin, are the only toxins in which their development, production, and stockpiling are also prohibited according to the Chemical Weapons Convention from 1993. Nevertheless, ricin has become a favorite tool of radical groups and individuals, and is related to several incidents over the last decades. The most famous one is the assassination of Georgi Markov using a gun disguised as an umbrella. Markov's story will be detailed later.

The ricin toxin was part of Iraq's weapon of mass destruction program between 1985 and 1991. About 10 liters of concentrated ricin solution was produced, and few artillery shells were filled with it for field testing (Zilinskas, 1997).

Between 1995 and 1997, several individuals were arrested in the United States for possessing ricin they had produced with homemade equipment. In addition, an extremist group in Minnesota was discovered and arrested for planning to kill a U.S. marshal using a mix of ricin with the solvent dimethyl sulfoxide (DMSO) (Franz and Jaax, 1997; Maman *et al*., 2003).

The latest incident was just at the beginning of 2003 when the British police uncovered a domestic laboratory that had already managed to produce a small quantity of ricin designated for use as weaponry (Mayor, 2003).

2.1. The Story of a "Death Umbrella"

Georgi Markov was a 49-year-old Bulgarian novelist and playwriter. He had to leave Bulgaria for London in the 1970s after he had put on a controversial play. In London, he had published and broadcasted anticommunist views. On September 7, 1978, while waiting in a bus station, he felt a painful blow to his right thigh. When he turned, he saw a man holding an umbrella. The next day, he was admitted to the hospital with a high temperature, vomiting, and difficulty in speaking. He appeared toxic, and had a 6-cm diameter region of inflammation and induration in his thigh. Three blood cultures were negative. His white blood cell count was 10,600/μL. The day after, he suffered from a septic shock-like syndrome with vascular collapse, and was sweating and dizzy. His white blood cell count rose to 26,300/μL. Afterward, he had stopped passing urine and the vomiting became bloody. Four days after the attack, his electrocardiogram showed complete conduction block. A few

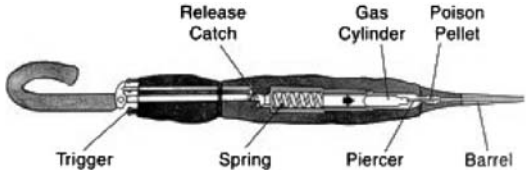

Figure 8.1. A schematic drawing of the umbrella used in Markov's assassination. [From Eitzen and Takafuji (1997), with permission from the publishers.]

hours later, he died. Autopsy revealed pulmonary edema, fatty change of the liver, hemorrhagic necrosis of the small intestines, and interstitial hemorrhage in the testicles, pancreas, and inguinal lymph nodes (Crompton and Gall, 1980).

Vladimir Kostov was another Bulgarian exile in Paris. On August 26, 1978, just 2 weeks before Markov's assassination, he felt a similar blow to his back while he was on the Metro. He also heard a sound like an air pistol shot. He had fever for which he was hospitalized for 12 days, and he recovered completely. X-ray showed a foreign body in his back. It was a tiny pellet. An identical one was removed from Markov's thigh (Crompton and Gall, 1980).

The metallic pellet was 1.5 mm in diameter, and it had two holes drilled through it. The holes were sealed with wax intended to melt at body temperature (Christopher *et al*., 1997; Crompton and Gall, 1980). Kostov wore heavy clothing so the pellet did not penetrate deep enough in his body for the wax coat to melt. It was estimated that the holes could have contained 500 μg of material inside. Although no substance was ever found in those two pellets, several agents – such as diphtheria toxin, clostridial toxin, and endotoxin – were considered to be possible causes. The circumstances suggested that it was probably ricin that was used

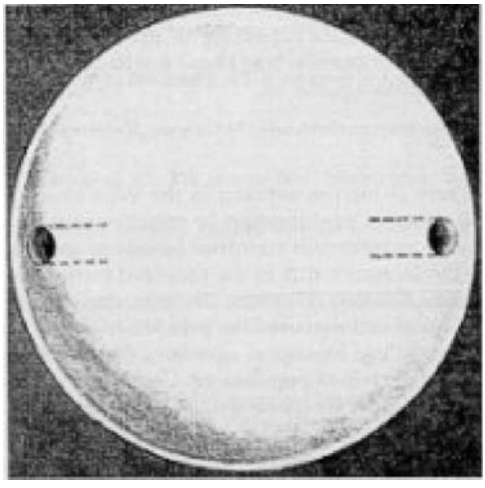

Figure 8.2. The tiny, cross-drilled and ricin-containing pellet that was removed from Markov's thigh after the assassination. [From Eitzen and Takafuji (1997), with permission from the publishers.]

in the attacks (Crompton and Gall, 1980). These two assasinations were said to have been carried out by the Bulgarian government. It was reported that the ricin was produced and sent to Bulgaria by the Soviet Union (Alibek, 1999).

3. THE TOXIN

The fibrous portion that remains after the extraction of oil from the castor bean contains the protein ricin – the most toxic substance in the plant kingdom (Ellenhorn, 1997).

Every year, a total amount of 1 million tons of castor beans are processed worldwide in the production of castor oil. One gram of ricin can be extracted from the waste mash, which remains after processing 1 kg of castor beans (Kortepeter *et al*., 2001).

Ricin is a 2.5 Å heterodimeric protein consisting of two glycoprotein chains of approximately equal molecular mass (~30 kDa) that are connected through a disulfide bridge. One chain (B) is a lectin that binds to a glycoprotein in the cell membrane, facili-

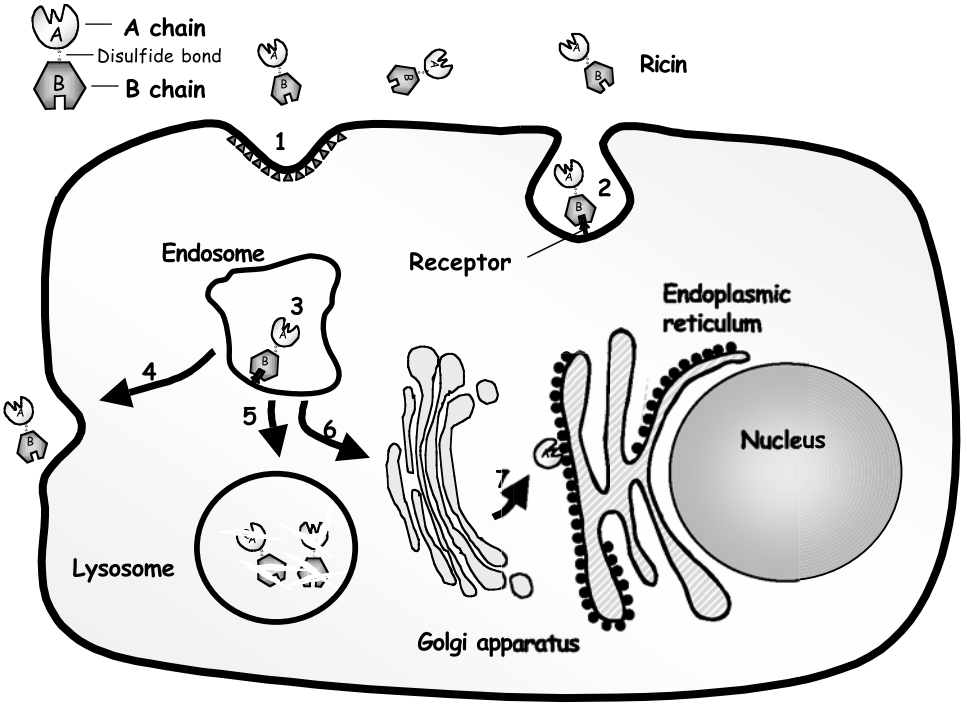

Figure 8.3. The pathway of ricin in the cell. Ricin binds to receptors with terminal galactose at either (*1*) coated pits or (*2*) smooth pits. (*3*) The ricin–receptor complex is endocytosed. (*4*) The complex can be recycled out of the cell or (*5*) transported to lysosomes for degradation. (*6*) Ricin A chain is transported to the *trans*-Golgi network. (*7*) Through the *trans*-Golgi apparatus, the A chain is transported to the endoplasmic reticulum, where it exerts its toxic effects on ribosomes.

tating endocytosis of the toxin to the cytosol. The other chain (A) has RNA *N*-glycosidase activity, removing a specific adenine base from 28S rRNA of the 60S ribosomal subunit, causing inactivation of the ribosome, preventing polypeptide elongation, and leading to cell death (Sandvig and Van Deurs, 2000).

Ricin is synthesized in the plant seeds as a single polypeptide, which is later cleaved into the A and B chains (Frigerio and Roberts, 1998; Kaku, 1998). The A chain is composed of 267 amino acids and the B chain is composed of 262 amino acids (Lord *et al*., 1994).

Ricin belongs to the group of type 2 ribosome inactivating proteins (RIPs). RIPs can be found in a wide variety of plants. Two types of RIPs are known. Type 1 RIPs are present in wheat and barley. They are not cytotoxic because they lack the means of entering the cell to inactivate ribosomes (Lord *et al*., 1994).

Type 2 RIPs, which have a galactose-binding lectin that assists cell entrance, is a group of extremely potent toxins that also includes the toxin abrin, isolated from the seeds of *Abrus precatorius* (or rosary pea) (Kaku, 1998; Lord *et al*., 1994).

Ricin's ability to bind both glycoproteins and glycolipids with terminal galactose, located on the cell surface, enables it to enter the cell exploiting all endocytosis mechanisms operating in the cell (Sandvig and van Deurs, 2002). On entering the cell inside an endosome, the toxin–receptor complex can be either delivered toward lysosomes where it would be destroyed or it can be recycled back to the cell surface. Apparently, only a small fraction of about 5% ricin will finally enter cytosol (Olsnes and Kozlov, 2001). It is not clear yet exactly when the disulfide bond is dissociated to yield the two separate chains A and B; yet, after it occurs, the A chain is taken up by the Golgi apparatus and transported retrogradely to the rough endoplasmic reticulum, where it exerts its toxic effect. In contrast, diphtheria and shiga toxins – which have a similar structure of two functionally different parts – enter the cytosol directly from the endosome (Olsnes and Kozlov, 2001).

The ricin A chain is a very efficient substance. Only one molecule is sufficient to block the cell's protein synthesis as a result of destroying about 2,000 ribosomes per minute. Thus, one molecule can kill the affected cell (Ellenhorn, 1997; Sandvig and van Deurs, 2002).

Ricin can be prepared and remain stable in various forms: liquid, crystalline, and even aerosol. Detoxification can be achieved by heating at 80°C for 10 minutes or 50°C for an hour at pH 7.8 or by chlorine [99.8% inactivation by 100 mg/L free available chlorine (FAC) for 20 minutes]. The toxin will remain stable in low chlorine concentrations (10 mg/L FAC) and in iodine at up to 16 mg/L (Kortepeter *et al*., 2001).

3.1. Toxicity

The toxicity of ricin is dependent on the route of exposure and the amount of the toxin that was administrated. Ricin is several hundreds times less toxic by ingestion than by parenteral administration, probably because of the enzymatic degradation in the digestive tract and poor absorption (Ellenhorn, 1997; Franz and Jaax, 1997; Maman *et al*., 2003).

Table 8.1
Toxicity of Ricin by Route of Exposure

		Ingestion	Inhalation	Intravenous injection	Subcoutaneous injection
Mice	LD_{50}	20 mg/kg[a]	3–5 μg/kg[a]	5 μg/kg[a]	24 μg/kg[a]
	Time to death (hrs)	85[a]	36–72[b]	90[a]	100[a]
Human	LD_{50}	30 μg/kg[c]	3 μg/kg[c]	3 μg/kg[c]	500 μg (based on Markov's assassination)
	Time to death	6–8 days	36–72 hrs[a, c]	36–72 hrs	3–6 days

[a] From Franz and Jaax (1997).
[b] Kortepeter *et al*. (2001).
[c] Mirarchi and Allswede (2003).

Ingestion of eight castor beans is said to be enough to kill a person (Ellenhorn, 1997). Fatal dose is considered as 5–6 castor beans for a child and 20 beans for an adult. Data concerning human toxicity is limited. It is based on reports describing animal experiments and accidental exposures of humans (Table 8.1).

4. RICIN AS A POTENTIAL BIOWEAPON

The Center for Disease Control and Prevention (CDC) listed ricin in category B of moderate threat biowarfare agents. Pathogens that pose a potential risk if used as a biological weapon are divided into three categories:

- **Category A agents** can be easily disseminated or transmitted from person-to-person, can cause high mortality, and have the potential for major public health impact. This category includes agents like smallpox, anthrax, plague, botulinum toxin, and Ebola hemorrhagic fever.
- **Category B agents** are moderately easy to disseminate, can cause moderate morbidity and low mortality, and include brucellosis, Q fever, glanders, ricin *Staphylococcus enterotoxin B*, and other pathogens that are food- or waterborne like Salmonella species and Shigella dysenteriae.
- **Category C agents** could be engineered for mass dissemination in the future because of availability, ease of production and dissemination, and potential for high morbidity and mortality and major health impact. This category includes yellow fever, multidrug-resistant tuberculosis, hantaviruses, and others (CDC, 2000).

Ricin is not an efficient weapon for mass destruction. Dispersion of ricin over a wide area is possible though logistically impractical. It is estimated that if eight metric tons of the toxin were scattered over a 100 km^2 area, about 50% of the population would die. In contrast, the same death toll could be "achieved" by using only kilogram quantities of

anthrax spores (Kortepeter and Parker, 1999). Castor beans' availability and the relative ease and inexpensive extraction in large quantities are factors that favor the use of ricin as a biological weapon in deliberate (terrorist) poisoning and assassinations. It can be injected into a target, used to contaminate food and water supplies, or can be dispersed as an aerosol (Kortepeter *et al*., 2001).

5. CLINICAL PRESENTATION

Castor beans are highly allergic and may cause anaphylaxis (Ellenhorn, 1997). The clinical presentation depends on the route of exposure.

1. **Gastrointestinal:** Rauber and Heard (1985) described more than 750 cases of intoxication following castor bean ingestion, 14 of them resulted in a fatality. This and other reports of serious cases of intoxication describes typical clinical manifestations (Challoner and McCarron, 1990; Rauber and Heard, 1985; Wedin *et al*., 1986). Allergic reaction may occur immediately after exposure (Ellenhorn, 1997). During the first few days following consumption of seeds, patients remain asymptomatic except for gradual loss of appetite and nausea. The most common initial symptoms result from gastrointestinal irritation and include burning in the alimentary tract, vomiting, diarrhea, and colicky abdominal pain. In severe poisoning, the symptoms progress to gastrointestinal bleeding with necrosis of the liver, spleen, and kidneys; dehydration; and even vascular collapse and shock. Children are more prone than adults to dehydration because of fluid losses through vomiting and diarrhea (Ellenhorn, 1997; Maman *et al*., 2003; Rauber and Heard, 1985).
2. **Parenteral administration:** Fostad *et al*. (1984) reported a clinical trial carried out on 54 cancer patients who were given intravenous injection of low-dose ricin (4.5–23 $\mu g/m^2$ of body surface area). Side effects were insignificant up to 18–20 $\mu g/m^2$, but 4–6 hours after administration of higher dose, flu-like symptoms with fatigue, muscular pain, nausea, and vomiting were observed and lasted for 1–2 days (Fodstad *et al*., 1984). Injection of a higher dose of ricin would cause vascular endothelial injury manifested by perivascular edema (Kortepeter *et al*., 2001).
3. **Inhalation:** The impact of inhaled ricin in rodents is characterized by necrosis of the upper and lower respiratory epithelium (Kortepeter *et al*., 2001). Symptoms emerge within 8 hours after inhalation and include fever, dyspnea, cough, respiratory distress, and nausea. Pulmonary edema, cyanosis, hypotension, respirataory failure, and circulatory collapse may be developing subsequently.
4. **Intramuscular injection:** At low doses, flu-like symptoms, myalgias, nausea, vomiting, and localized pain and swelling at the injection site are expected. Severe intoxication causes also muscle and regional lymph node necrosis, as well as visceral organ involvment (gastrointestinal hemorrhage, diffuse hepatic, splenic, and renal necrosis) described in Markov's assassination.
5. **Dermal exposure:** Dermal exposure is usually insignificant because of poor absorption through the skin unless enhanced with a strong solvent like DMSO.

5.1. Prognosis

Death from ricin intoxication could occur within 36–48 hours, independent of the route of exposure. If death has not occurred within 3–5 days, the patient usually survives. The study of Rauber and Heard (1985) described a mortality rate of 1.9% (14 of 751 patients) after castor bean ingestion. This rate is lower than previously known. Mortality rate from inhalation of ricin in humans is unknown, but potentially could be substantially higher.

5.2. Diagnosis

The diagnosis of ricin poisoning can be made on a clinical and epidemiological basis. Ricin intoxication should be suspected if a cluster of cases with acute lung injury has occurred. A covert dispersion of aerosolized ricin is expected to be diagnosed, post factum, only after clinical symptoms occur (Kortepeter *et al*., 2001). Confirmation of ricin exposure is possible by ELISA analysis of nasal or throat swabs. The CDC can detect ricin in environmental specimens using a time-resolved fluorescence immunoassay.

- **Laboratory findings:** Patients may present with neutrophilic leukocytosis, arterial hypoxemia, bilateral infiltrates on chest radiograph, and protein-rich bronchial aspirate (Maman *et al*., 2003; Mirarchi and Allswede, 2003). Identification of the toxin in body fluids is very difficult. ELISA may be useful (Shyu *et al*., 2002). Being immunogenic, ricin is expected to induce an antibody response. Thus, antibody level should be measured in the sera of patients 2 weeks after exposure (Franz and Jaax, 1997). A polymerase chain reaction is done only at CDC to detect the DNA of the gene that produces the ricin toxin in environmental samples.
- **Differential diagnosis:** Differential diagnosis includes community-acquired pneumonia, staphylococcal enterotoxin B, inhalational anthrax, oxides of nitrogen and phosgene, Q fever and tularemia. If antibiotic treatment did not halt progress of symptoms, an infectious agent should be ruled out – thus suggesting ricin intoxication (Kortepeter *et al*., 2001). Table 8.2 compares symptoms and clinical signs, and X-ray and laboratory findings of three major differential diagnoses: community-acquired pneumonia, inhalational anthrax, and inhalational ricin intoxication.

6. TREATMENT

There are no antidotes for ricin. Prevention of exposure is always best. Aerosol exposure can be effectively prevented using a protective mask. Treatment is basically supportive and depends on the route of exposure and clinical manifestations. Symptomatic patients

Table 8.2
Comparison of Signs and Symptoms, X-ray, and Laboratory Findings of Three Major Differential Diagnoses

	Inhalational ricin intoxication	Community-acquired pneumonia	Inhalational anthrax
Signs and symptoms	Fever Dyspnea Cough Respiratory distress Nausea Cyanosis Hypotension Respiratory failure	Cough Sputum production Dyspnea Tachypnea Cyanosis Bronchial breath Pleuritic chest pain Fever	Flu-like symptoms (fever and chills, muscle aches and headaches) Nonproductive cough Nausea and vomiting Dyspnea Chest discomfort Headache Tachycardia Respiratory failure Shock Meningitis may develop
X-ray	Bilateral infiltrates Pulmonary edema	Pulmonary infiltrates	Mediastinal widening Pleural effusion
Laboratory findings	Neutrophilic leukocytosis	Leukocytosis	Neutrophilic leukocytosis Elevated transaminases *Bacillus anthracis* growth in blood cultures

require hospitalization for supportive care, fluids, and electrolyte replacement. Ricin is water-soluble, and little is extracted in the urine. Therefore, there is no indication for hemodialysis or induced diuresis (Ellenhorn, 1997).

1. **Ingestion:** Effort should first be taken to prevent ricin absorption. This should include gastric emptying/lavage, syrup of ipecac, cathartics, and some even recommend the use of activated charcoal (Ellenhorn, 1997; Maman *et al*., 2003). If the patient chewed some beans and presented asymptomatic, he should remain under observation for 4–6 hours after ingestion (Ellenhorn, 1997).
2. **Inhalation:** Respiratory support is given as needed. The patient may require treatment of pulmonary edema and the use of positive end-expiratory pressure (Kortepeter *et al*., 2001).
3. **Dermal exposure:** Supportive treatment.

7. PREVENTION AND VACCINE

Prevention: Early detection of the toxin is essential to promote an adequate response. Several locations in the United States, like government and U.S. Postal Service offices, use sensors for detection of chemical and biological agents, such as ricin. If ricin is suspected

to be present, a sample is referred for confirmation in a reference laboratory (Centers for Disease Control and Prevention, 2003). When entering a contaminated area, one should wear adequate personal protective equipment, especially a protective mask as protection against inhalation. Health care workers should use standard precautions when treating a patient with ricin intoxication.

Vaccine: No vaccine is currently available. Experimental vaccines are under development and have shown effectiveness in animals (Kende *et al.,* 2002; Yan *et al*., 1996). Two vaccines have been used to confer complete protection against inhalation exposure: toxoid-formalin inactivated toxin and deglycosylated ricin toxin A unit. Nonetheless, inactivation of the toxin by formalin is not complete, and the preparations still have residual toxic effect (Smallshaw *et al*., 2002). Smallshaw *et al*. (2002) developed novel mutant and non-toxic ricin toxin A unit that protected mice exposed to 10 times mice LD_{50} of ricin.

The latest report in September 2004 (Hampton, 2004) indicated that US Army scientists have developed a new experimental vaccine that is safe and protective in mice. Further animal studies are planned in the future in order to achieve a vaccine safe to humans.

8. MEDICAL USE OF RICIN

Ricin, being constructed of two parts, one of which has a receptor-binding capability, is used to develop novel therapeutics, such as immunotoxins (Oeltmann and Frankel, 1991; Weissmann-Brenner *et al., 2002*). The receptor-binding B moiety can be replaced by either antibodies to targets, such as cancer-associated antigens, or by other binding proteins like hormones or growth factors. The new-bound protein should have the same affinity to be guided to the endoplasmic reticulum through the *trans*-Golgi network to reach the ribosomes (Kreitman, 1999, 2001).

9. CONCLUSION

Ricin is a potent and easy to extract plant toxin. Its characteristics make it a potentially dangerous biological weapon. We understand now, better than ever, the pathogenesis of ricin poisoning. But treatment of ricin poisoning is still mainly supportive. More research is needed to develop specific and effective modalities of treatment.

The threat of bioterrorism is no longer as remote as it was in the past. The medical community should be familiar with the clinical presentation and treatment of ricin poisoning. Knowledge will allow better recognition and response to an attack.

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