

# Ricin Poisoning

## A Comprehensive Review

Jennifer Audi, MD

Martin Belson, MD

Manish Patel, MD, MSc

Joshua Schier, MD

John Osterloh, MD, MS

**G**ROWING AWARENESS AND concern about ricin, a potent biologic toxin, as a possible terrorist weapon has necessitated a comprehensive review of this poison.<sup>1</sup> The Centers for Disease Control and Prevention (CDC) categorizes ricin as a Category B agent (second-highest priority), as it is moderately easy to disseminate, resulting in low mortality but moderate to high morbidity, and requires specific enhancement of the CDC's diagnostic and disease surveillance capacity.<sup>2</sup> Such agents are not routinely encountered, so heightened awareness in the health care community and a strong public health infrastructure are necessary for detection and response. We therefore have summarized the literature on ricin poisoning and provided recommendations for clinicians and public health professionals dealing with a ricin attack against a civilian population.

### EVIDENCE ACQUISITION

Using PubMed, we searched MEDLINE and OLDMEDLINE databases from January 1950 to August 2005 using the keywords *ricin*, *ricinus communis*, *ricinine*, *plant toxins*, *castor beans*, *castor dust*, and *castor oil*. Keywords were used alone and with the modifiers *toxicity*, *poisoning*, *diagnosis*, *clinical effects*, *treat-*

**CME available online at**  
[www.jama.com](http://www.jama.com)

**Context** The recent discoveries of ricin, a deadly biologic toxin, at a South Carolina postal facility, a White House mail facility, and a US senator's office has raised concerns among public health officials, physicians, and citizens. Ricin is one of the most potent and lethal substances known, particularly when inhaled. The ease with which the native plant (*Ricinus communis*) can be obtained and the toxin extracted makes ricin an attractive weapon.

**Objectives** To summarize the literature on ricin poisoning and provide recommendations based on our best professional judgment for clinicians and public health officials that are faced with deliberate release of ricin into the environment.

**Literature Acquisition** Using PubMed, we searched MEDLINE and OLDMEDLINE databases (January 1950-August 2005). The Chemical and Biological Information Analysis Center database was searched for historical and military literature related to ricin toxicity. Book chapters, unpublished reports, monographs, relevant news reports, and Web material were also reviewed to find nonindexed articles.

**Results** Most literature on ricin poisoning involves castor bean ingestion and experimental animal research. Aerosol release of ricin into the environment or adulteration of food and beverages are pathways to exposure likely to be exploited. Symptoms after ingestion (onset within 12 hours) are nonspecific and may include nausea, vomiting, diarrhea, and abdominal pain and may progress to hypotension, liver failure, renal dysfunction, and death due to multiorgan failure or cardiovascular collapse. Inhalation (onset of symptoms is likely within 8 hours) of ricin is expected to produce cough, dyspnea, arthralgias, and fever and may progress to respiratory distress and death, with few other organ system manifestations. Biological analytic methods for detecting ricin exposure are undergoing investigation and may soon be available through reference laboratories. Testing of environmental samples is available through federal reference laboratories. Currently, no antidote, vaccine, or other specific effective therapy is available for ricin poisoning or prevention. Prompt treatment with supportive care is necessary to limit morbidity and mortality.

**Conclusion** Health care workers and public health officials should consider ricin poisoning in patients with gastrointestinal or respiratory tract illness in the setting a credible threat. Poison control centers and public health authorities should be notified of any known illness associated with ricin exposure.

JAMA. 2005;294:2342-2351

[www.jama.com](http://www.jama.com)

*ment, warfare, chemical terrorism, and weapon.* The Chemical and Biological Information Analysis Center (<http://www.cbiac.apgea.army.mil>) data-

base was searched for historical and military literature related to ricin tox-

**Author Affiliations:** Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Environmental Hazards and Health Effects, Health Studies Branch (Drs Audi, Belson, Patel, and Schier) and National Center for Environmental Health, Division of Laboratory Sciences (Dr Osterloh), Emory University, Department of Emergency Medicine and Georgia Poison Control Center, Section of Toxicology (Drs Audi, Belson, Patel, and Schier), Atlanta.

Dr Audi is now at the Nebraska Regional Poison Center and the Department of Surgery of the University of Nebraska Medical Center, Omaha.

**Corresponding Author:** Jennifer Audi, MD, Nebraska Regional Poison Center, 8401 W Dodge Rd, Suite 115, Omaha, NE 68154 ([cza7@cdc.gov](mailto:cza7@cdc.gov)).

**Clinical Review Section Editor:** Michael S. Lauer, MD. We encourage authors to submit papers for consideration as a "Clinical Review." Please contact Michael S. Lauer, MD, at [lauer@cfcf.org](mailto:lauer@cfcf.org).

icity. References cited in the retrieved articles were also evaluated to find non-indexed reports. Because much information regarding ricin as a chemical warfare agent is not in the peer-reviewed literature, book chapters, unpublished reports, monographs, relevant news reports, and Web material available in the authors' collections were also reviewed. The information provided herein is our best professional judgment regarding the clinical and public health implications of use of ricin as a chemical warfare agent. These recommendations should be reassessed as new information becomes available.

## EVIDENCE SYNTHESIS

### Description

**Ricin.** Purified ricin is a white powder that is soluble in water and stable over a wide pH range.<sup>3,4</sup> It is inactivated by heat, 80°C in aqueous solution for 1 hour,<sup>4</sup> and requires higher temperatures or longer periods for inactivation when in powder or crude forms. It is a protein toxin (ie, toxalbumin) derived from the castor bean plant, *Ricinus communis* (FIGURE 1 and BOX 1) and has a molecular weight of 60 to 65 kDa.<sup>5</sup> Reports on the ricin content of castor beans vary but probably is in the range of 1% to 5%.<sup>5,6</sup> Ricin is being studied for therapeutic use in cancer chemotherapy, in bone marrow transplantation, and in cell-based research.<sup>7-12</sup> Experimental evidence suggests that malignant cells are more susceptible to ricin toxicity because they express more carbohydrate-containing surface-lectin binding sites than do nonmalignant cells.<sup>9-11</sup> Antibody-conjugated ricin targets cancer cells and has been investigated as an immunotherapeutic agent.<sup>6-13</sup>

**Castor Beans.** The beans are oblong and light brown, mottled with dark brown spots (Figure 1). They are used to produce castor oil that is used in paints, varnishes, and lubricating oils for jet engines, high-speed automobiles, and industrial machinery.<sup>14</sup> Another use of castor oil is as a purgative. Ricin is contained in the bean pulp fol-

**Figure 1.** Ricin Plant *Ricinus communis* and Castor Beans (*Ricinus communis* Seeds)



lowing the separation of the oil from the beans. No ricin is thought to remain in the oil, and ricin is inactivated during oil extraction if done under heated conditions.<sup>4,15</sup> Ingested castor beans are generally toxic only if ricin is released through mastication or maceration.<sup>16</sup> The roots, leaves, and seeds of the plants are also used in traditional or folk remedies throughout the world.<sup>17</sup>

### Historical Use of Ricin and Emerging Threats

The US War Department considered ricin for chemical warfare as early as 1918.<sup>3</sup> Ricin was tested as an inhalational agent in the 1940s.<sup>18</sup> Although never laboratory-confirmed, it was most likely the etiologic agent used in the 1978 assassination of Bulgarian journalist Georgi Markov in Great Britain.<sup>19,20</sup> In the 1940s in the United States and in late 1980s in Iraq, weapons-grade ricin (ie, purified and inhalable particles that can be aerosolized for a mass attack) was manufactured and tested in animal experiments and in artillery shells in field testing.<sup>4,21</sup>

In 2003 and 2004, ricin was discovered in a South Carolina mail sorting facility, a mailroom serving US Senator Bill Frist's office, and inside a letter addressed to the White House.<sup>1</sup> Ricin has also been discovered in the possession of persons affiliated with antigovernment groups and outside the United States in the possession of individuals possibly linked to terrorist organizations.<sup>22,23</sup>

### Routes of Dissemination

The physical state and dissemination method for ricin will determine its route of exposure in humans. Ricin can be prepared as a crude impure plant extract, purified crystals or powder forms, or solubilized in liquids. Deliberate dissemination may occur as an aerosol, through addition to food or water, or by direct parenteral injection. Airborne dispersal of ricin in the low micron-sized particle range is known to have been tested in the military setting, though there is little written information.<sup>3,4,18</sup> Ricin is unlikely to be persistent in the environment, but low micron-sized particles may stay suspended in undisturbed air for many hours and resuspension of settled low micron-sized particles from disturbed surfaces can occur.<sup>4</sup> Particles less than 10 μm have been used for aerosol inhalation animal studies, with potency increasing as particle size decreases to about 1 μm.<sup>3,24,25</sup> Ricin poisoning is not contagious and person-to-person transfer is unlikely.<sup>11</sup>

### Mechanism of Action

Ricin is a glycoprotein lectin composed of 2 chains, A and B, linked by a disulfide bond.<sup>13,26</sup> The B chain is a lectin and binds to galactose-containing glycoproteins and glycolipids expressed on the surface of cells, facilitating the entry of ricin into the cytosol.<sup>13,26-32</sup> The A chain inhibits protein synthesis by irreversibly inactivating eukaryotic ribosomes through removal of a single adenine residue from the 28S ribosomal RNA loop

### Box 1. Background, Diagnosis, Treatment, and Prevention and Reporting of Ricin Poisoning\*

#### Background

Ricin is a toxin derived from the castor bean plant *Ricinus communis*.

Poisoning can occur via ingestion, inhalation, or injection.

Ricin poisoning can have a presentation similar to gastroenteritis or respiratory illnesses.

Epidemiologic clues include increased number of patients seeking care, unexpected progression of symptoms, or a credible threat of ricin release in the community.

Person-to-person transmission does not occur.

Ricin has been procured for use as a terrorist weapon.

Inhalation and injection are considered to be the most lethal routes of exposure.

#### Clinical Findings

**Ingestion:** Mild poisoning can result in nausea, vomiting, diarrhea, and/or abdominal pain. In moderate to severe poisoning, gastrointestinal tract symptoms can progress (4-36 hours) to hypotension, liver and renal dysfunction, and possibly death.

**Inhalation:** Illness can occur within 8 hours and include cough, dyspnea, arthralgias, and fever, and can progress to respiratory distress and death.

**Injection:** Initial (ie,  $\leq 6$  hours) symptoms can include generalized weakness and myalgias; progression of illness (24-36 hours) can include vomiting, fever, hypotension, and/or multiorgan failure and death.

#### Laboratory Testing

No clinically validated methods are available to detect ricin in biological fluids.

Analytic methods for detecting ricin (in blood) and ricinine (in urine) may be available through reference laboratories (the US Army Medical Research Institute for Infectious Diseases and the Centers for Disease Control and Prevention) in an emergency response setting.

Centers for Disease Control and Prevention and Laboratory Response Network laboratories conduct tests to detect ricin in environmental samples.

#### Recommended Treatment

Treatment is mainly supportive and includes intravenous fluid and vasopressors (eg, dopamine) for hypotension.

Activated charcoal should be administered to persons with known or suspected ricin ingestion if vomiting has not begun and airway is secure.

Gastric lavage may be considered if ingestion has occurred in an hour or less.

If a credible threat exists, patients with illness consistent with ricin poisoning should be observed for illness progression.

The regional poison control center should be contacted for individualized care and further management.

#### Prevention and Reporting in the United States

All known or suspected cases of ricin exposure should be reported to the regional poison control center ([800]222-1222) and local and state health departments.

\*This is a modified version of an original figure in *MMWR*.<sup>1</sup>

contained within the 60S subunit. This process prevents chain elongation of polypeptides and leads to cell death (FIGURE 2).<sup>32-37</sup> Toxicity results from the inhibition of protein synthesis, but other mechanisms are noted including apoptosis pathways, direct cell membrane damage, alteration of membrane structure and function, and release of cytokine inflammatory mediators.<sup>28,38-45</sup> A broad group of bacterial and plant toxins have A- and B-chain protein components, such as diphtheria, ricin, botulinum, and anthrax. Ricin belongs to a group of 2-chain toxins possessing ribosomal-inactivating-protein activity (classified as RIP-II) in their A chains, along with such toxins as shigatoxin, abrin, modeccin, volkensin, and viscumins. Some other plant proteins have no B chain binding component, such as gelonin, trichosantin, and momordin but possess the catalytic RIP activity and are classified RIP-I.<sup>13</sup>

The castor bean plant also contains another glycoprotein lectin, the ricin communis agglutinin, which, unlike ricin, is not directly cytotoxic but does have affinity for the red blood cell, leading to agglutination and subsequent hemolysis. Ricin communis agglutinin is not significantly absorbed from the gut and causes clinically significant hemolysis only after intravenous administration.<sup>4,5,19,20,36,44,46</sup>

Ricinine is an alkaloidal toxin also found in the leaves and pericarp of the castor bean plant. Although small amounts of ricinine are found in the castor bean and can be coextracted with ricin, there are no reports of human ricinine poisoning.<sup>47</sup> In experimental mice models, ricinine causes convulsions and subsequent death; the mechanism of action is hypothesized to be increased release of glutamate and inhibition of the postsynaptic  $\gamma$ -aminobutyric acid receptor subtype A in the brain.<sup>48-50</sup>

#### Toxicokinetics/Toxicodynamics and Clinical Effects in Animals and Humans

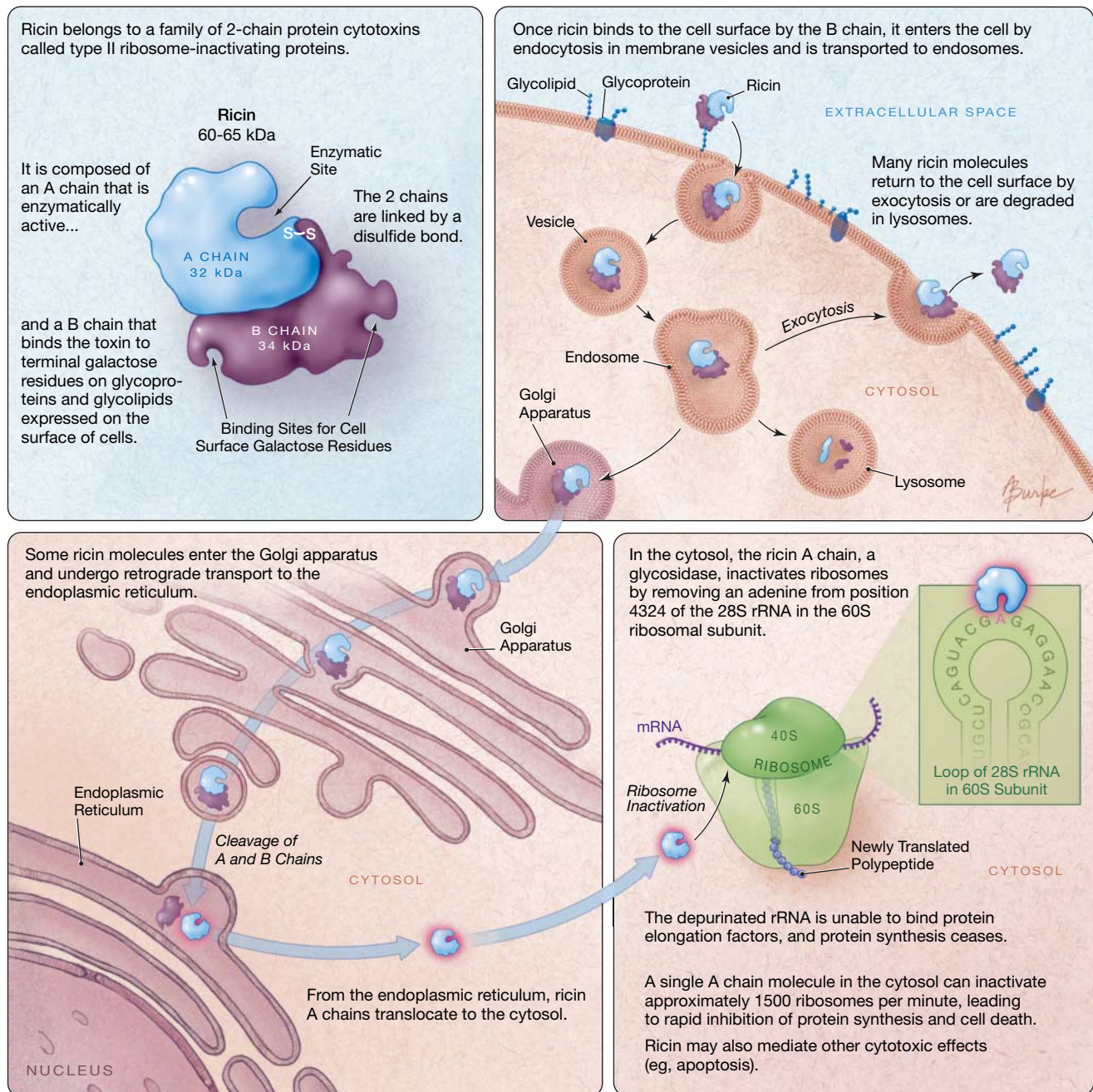
**Ingestion.** *Toxicokinetics/Toxicodynamics.* There are no literature reports of

poisoning from ingesting purified ricin. All clinical reports with regard to poisoning refer to castor bean ingestion. The median lethal dose (LD<sub>50</sub>) in mice is 30 mg/kg, or approximately 1000-fold higher than by injection or inhalation. In previous reports of human castor bean ingestion, the lethal

oral dose in humans has been estimated to be 1 to 20 mg of ricin/kg of body weight (approximately 8 beans); but ricin doses estimated from the number of beans ingested may give inaccurate estimates due to variation in the size, weight, and moisture content of the beans; region, season, and period

of plant growth at time of harvest of the beans; as well as the degree of mastication, age, and comorbidities.<sup>5,6,14,16,50-53</sup> The number of beans ingested in reports documenting clinical symptoms (mild to lethal) range from one half to 30.<sup>16,52</sup> The minimum number of beans associated with death was 2.<sup>16</sup>

**Figure 2.** Mechanism of Ricin Toxicity



In animal studies, ingested ricin is absorbed within 2 hours by both lymphatic and blood vessels, accumulates mainly in the liver and spleen, and approximately 20% to 45% is excreted unchanged in the feces up to 72 hours after ingestion.<sup>54,55</sup>

**Clinical Effects.** Symptom onset after ingestion is usually within 4 to 6 hours but may be as late as 10 hours.<sup>16,51-53,56-65</sup> Initial symptoms are nonspecific and may include colicky abdominal pain, vomiting, diarrhea, heartburn, and oropharyngeal pain. Hematemesis and melena are reported less commonly.<sup>16,51,52,56,59</sup> Fluid losses may lead to electrolyte imbalances, dehydration, hypotension, and circulatory collapse.<sup>16,51-53,56,58,60</sup> Laboratory abnormalities may include leukocytosis, elevated transaminases and creatinine kinase, hyperbilirubinemia, renal insufficiency, and anemia.<sup>16,59,61-63</sup>

Postmortem findings of diffuse intestinal hemorrhagic lesions as well as histology consistent with the appearance of apoptotic cell death are seen in both humans and animals.\*

**Injection.** *Toxicokinetics/Toxicodynamics.* Little published data on human exposure to ricin by parenteral routes exist. The LD<sub>50</sub> in mice is approximately 5 to 10 µg/kg.<sup>9,67</sup> Minimum lethal doses range from 0.7 to 2 µg/kg in mice and 1 to 1.75 µg/kg in dogs.<sup>68</sup> After injection in rodents, the majority of ricin excretion occurs in the urine over the first 24 hours, with less than 2% recovered in feces.<sup>69,70</sup>

**Clinical Effects.** The onset of nonspecific signs and symptoms, which may be similar to sepsis (fever, headache, dizziness, nausea, anorexia, hypotension, abdominal pain), can be delayed for as much as 10 to 12 hours, even with high doses.<sup>9,67,68</sup> There may also be local tissue damage at the site of the injection. Laboratory abnormalities include elevated liver transaminases, amylase, and creatinine kinase, hyperbilirubinemia, myoglobinuria, and renal insufficiency.<sup>71,72</sup> The clinical course may progress to multisystem organ failure.<sup>5,6,8,71,72</sup>

Postmortem findings are consistent in case investigations and animal studies and include focal hemorrhage in the intestines, brain, myocardium, and pleura.<sup>9,51,67,71,72</sup> Lymph nodes, kidneys, and intestines may also demonstrate necrosis, hemorrhage, and edema.<sup>9,38-41,69,70,73-75</sup>

**Inhalation.** *Toxicokinetics/Toxicodynamics.* Lung deposition and lethality after ricin inhalation is significantly influenced by particle size. Particles of low micron-size can deposit deeper into the respiratory tract resulting in higher mortality.<sup>76</sup> Particles of increasingly larger diameter typically deposit higher in the airways and can be swept up by the mucociliary system and subsequently swallowed.<sup>24</sup> The LD<sub>50</sub> in mice exposed to ricin of particle sizes less than 5 µm is about 3 to 5 µg/kg.

Monkeys exposed to inhaled ricin developed progressive dyspnea 20 to 24 hours after 21 to 42 µg/kg dosing of 1- to 2-µm particles.<sup>77</sup> Three of the 5 monkeys died at 36, 40, and 48 hours. Postmortem findings included diffuse pulmonary edema with multifocal areas of necrosis and inflammation.<sup>76-78</sup> All injury was significantly worse in the distal airways and alveoli.

Toxicity results from the inhibition of protein synthesis, release of cytokine mediators, and direct injury to the epithelial membrane.<sup>76,79</sup> The primary target of toxicity after ricin inhalation are the type I and II pneumocytes.<sup>76-78</sup> There was no significant systemic absorption after inhalational exposure and toxicity was primarily limited to the respiratory tract in these animal studies.<sup>24,25,76</sup>

**Clinical Effects.** Respiratory failure is likely to be the primary cause of morbidity and mortality in humans after inhaling ricin. Only 1 poorly documented report exists of inhalational ricin poisoning in humans. In the 1940s, 8 persons developed fever, nausea, cough, dyspnea, chest tightness, and arthralgias within 4 to 8 hours of presumed inhalational exposure to uncharacterized ricin-containing material.<sup>18</sup> Based on this report and animal studies, patients may exhibit respira-

tory symptoms as soon as 4 to 6 hours, but delays in the onset of serious symptoms are considered possible up to 24 hours after exposure.<sup>18,77</sup>

Airborne ricin exposure may also cause an allergic response leading to reactive airway inflammation, rhinitis, and ocular irritation. However, information on allergic reactions to ricin is primarily in persons working in or living near castor bean processing plants.<sup>80-85</sup> Allergy patch testing reveals an IgE-mediated inflammatory reaction to ricin although other allergens may be present in the castor bean dust.<sup>83,86-89</sup> No cases consistent with direct respiratory tract injury have been reported in the occupational setting, most likely because of the larger particle size of ricin in the castor bean dust or heat inactivation of the plant material.

**Dermatologic/Ophthalmologic.** An urticarial, IgE-mediated, allergic reaction may occur after handling of the intact castor bean plant or exposure to the castor bean dust or pomace.<sup>83,86-90</sup> Irritation and the development of pseudomembranous conjunctivitis after ocular exposure to very low ricin concentrations is reported in animals.<sup>3,91</sup>

### Laboratory Detection

**Biological Specimens.** In animal studies, ricin has been detected in tissue sections, some tissue specimens, nasal swabs, and fluids by immunologically based methods.<sup>53,92,93</sup> Immunologically based methods have been applied to human and animal fluid specimens in the past and have the potential to measure concentrations as low as 0.1 ng/mL (1.54 pmol/L).<sup>93-98</sup> However, such applications have not been clinically validated and concentrations after toxic exposures are unknown. Reference laboratories (eg, US Army Medical Research Institute of Infectious Diseases and the CDC) are currently adapting these and other analytic methods for application to human specimens. Matrix-assisted laser desorption-ionization mass spectrometry (MALDI-MS) holds promise as a definitive method for identification in biological specimens. In suspected

\*References 5, 6, 14, 16, 38-40, 51, 52, 66.

cases, clinicians should collect urine and serum samples and contact their state public health department or CDC for further guidance. Currently, there is no widely available commercial assay for ricin in biological samples.

A urine assay for detecting the alkaloid ricinine also holds future potential for diagnosing ricin exposure.<sup>46,99</sup> Because ricinine and ricin are extracted from the same plant source, ricinine may serve as a surrogate marker for the presence of ricin. Detection of ricinine up to 48 hours after exposure may be possible with newer methods available at the CDC.<sup>99</sup>

**Environmental Specimens.** The CDC and Laboratory Response Network laboratories conduct polymerase chain reaction tests and time-resolved immunofluorescence assays to detect ricin in environmental specimens. Cell-based bioassays are sometimes used to confirm intact toxin-killing activity of the ricin in environmental samples. Field immunoassays (so-called Hand-Held-Assay, or “smart tickets”) have been available to the military. As with other preliminary testing, confirmatory testing is required. Other field test kits are under development for the US Department of Homeland Security and the various branches of the US military, but commercial distribution is limited.

### Immunity

Animal studies have demonstrated the possibility of protection against inhalational and parenteral ricin poisoning through passive immunization (ie, ricin-specific antibodies) or active immunization with a ricin vaccine.<sup>100,101</sup> Passive immunization affords protection against inhalational ricin if administered prior to exposure; however, the benefit of postexposure immunization remains undefined.<sup>100,102,103</sup> Several animal studies have investigated active immunization and demonstrated that adequate levels of ricin-neutralizing protective antibodies would be maintained.<sup>104-107</sup>

Two preparations of ricin have been used for vaccination: formaldehyde-inactivated ricin (toxoid) and deglyco-

## Box 2. Personal Protective Equipment Recommendations for First Responders and Health Care Workers Responding to a Suspected Ricin Event

### Field and First Responders

Entering a contaminated area where aerosolized ricin is suspected, personal protective equipment (PPE) should be level B and include self-contained breathing apparatus\*

Decontaminating patients away from site of release†

Disposable Tyvek suit coated with a chemical to prevent penetration (eg, Saran or polyethylene)

Air purifying respirator with P-100 filter<sup>108</sup>

Eye and face protection (eg, full-face respirator)

Decontamination of PPE (after patient care and scene management tasks are completed)

Outside of the PPE should be washed with water before careful removal to prevent resuspension of particles†

After PPE removal, first responders should shower<sup>108</sup>

Nondisposable PPE should be decontaminated thoroughly by rinsing with soap and water<sup>108</sup>

Soak equipment (including nondisposable PPE) in a 0.1% sodium hypochlorite solution for 30 minutes, rinse with soap and water and allow to air dry<sup>15,108,109</sup>

### Hospital and Health Care Workers

Decontamination of contaminated patients should occur outside the hospital or in designated hazardous materials (HAZMAT) decontamination areas

Personal protective equipment as above for first responders decontaminating patients away from site of release.

Following universal precautions is adequate while treating decontaminated patients

\*Initially the exact nature of contaminant(s) may not be known and higher levels of PPE may be required; see detailed guidance at the Web site of the US Occupational Safety and Health Administration ([http://www.osha.gov/dts/osta/bestpractices/html/hospital\\_firstreceivers.html](http://www.osha.gov/dts/osta/bestpractices/html/hospital_firstreceivers.html)) or the Interim Recommendations for the Selection and Use of Protective Clothing and Respirators Against Biological Agents, at <http://cdc.gov/niosh/unp-intrecppe.htm>. Pressure demand, self-contained breathing apparatus is recommended in response to nonroutine emergency situations (chemical, biological, radiological, and nuclear environment certified, if available).<sup>108</sup>

†Resuspension of ricin powder (when <50 μm) during decontamination and droplet contact with broken skin or mucous membranes may be secondary exposure pathways.

sylated ricin A chain. However, a specific vaccine produced by recombinant technology, RiVax (DOR BioPharma Inc, Miami, Fla), is highly purified and induces high titers of neutralizing antibodies in animals. Phase 1 clinical trials in humans should begin in 2005.<sup>101</sup>

### Personal Protective Equipment and Decontamination

The primary hazard from entering a contaminated area involves particu-

late matter inhalation through primary aerosolization—the period when ricin particles are first made airborne. Ricin inhalational toxicity depends on particle size. In general, particles larger than 10 μm do not reach bronchiolar-alveolar levels and are unlikely to pose a serious inhalational hazard.<sup>4,76-78,104,107</sup>

However, determination of particle size at the scene is usually not possible prior to entry. Other important determinants of inhalational toxicity that war-

### Box 3. Decontamination Recommendations for Patients With Ricin Exposure\*

#### Dermal\*

Make the patient "as clean as possible" after life-threatening issues have been addressed<sup>108,109</sup>

Remove contaminated clothing and jewelry

Wash skin with soap and copious amounts of water

Double bag and label belongings as contaminated

#### Oral

Single dose of activated charcoal<sup>110</sup>

Gastric lavage is of limited efficacy but can be considered if patient presents within 1 hour of ingestion<sup>111</sup>

#### Inhalational

Remove patient from exposure

Gut decontamination is not necessary†

#### Environmental Contamination

Clean surfaces and clothing with a 0.1% sodium hypochlorite solution for 30 minutes; will inactivate more than 99% of ricin<sup>15,108,109</sup>

Clean carpets with steam and HEPA filtering<sup>108,109</sup>; however, given the paucity of data available, it may be most prudent to remove the contaminated carpet

\*Low volatility of ricin and negligible absorption through intact skin poses minimal risk of toxicity to the exposed patient or to a health care worker.

†Unintentional ingestion of ricin after inhalational exposure is unlikely.

rant consideration before an informed decision regarding personal protective equipment can be made include: ricin purity; risk after secondary aerosolization from ground or other surfaces; duration of particle suspension in air; and method of dispersal (eg, aerosolization through ventilation system vs explosive release); and time since release. No evidence exists regarding the level of respiratory protection necessary to prevent inhalational toxicity. In a response setting during which information is limited and a credible threat exists, conservative precautions should be taken (BOX 2).

Data and experience are limited regarding approaches to skin or gut decontamination of victims following a ricin release (BOX 3). Recommendations for decontamination are based on inference from information on ricin's chemical and physical properties, exposure route, and best judgment using a prudent clinical and public health

approach. The chemical and physical properties of ricin suggest that after decontamination is completed, patients and health care workers are not at risk for ricin poisoning from secondary contamination (ie, body fluids).

### Diagnosis, Management, Disposition, and Prognosis

Recognition of the ricin poisoned patient will likely be difficult due to similarities with more commonly encountered illnesses (BOX 4). Diagnosis will rely on the clinician's suspicion in the context of a credible ricin threat or in the context of an outbreak of severe gastrointestinal or respiratory illness.<sup>1,16,113</sup>

**Diagnosis.** Oral ricin exposure will lead to a syndrome resembling foodborne, chemical or infectious gastroenteritis (Box 4). Following exposure, onset of gastrointestinal symptoms may occur within a few hours of exposure, mimicking some

infectious and chemical agents. A dose-dependent spectrum of illness may be expected ranging from mild symptoms to profuse diarrhea (possibly bloody), dehydration, hypotension, and multisystem organ failure. Severe gastrointestinal illness or a rapid progression should heighten the suspicion for ricin exposure. Similarly, rapid progression of severe respiratory illness over 12 to 24 hours, after unknown inhalational exposures, may increase the concern for ricin although a number of noxious chemicals can produce injury in this time frame (Box 4).

**Management.** No specific treatment protocols exist for ricin exposures; treatment is largely symptomatic and supportive. To prevent further systemic absorption of unknown toxic substances, a single-dose of activated charcoal should be considered for non-vomiting patients, even though adsorption of ricin by charcoal is unknown (Box 3).<sup>110</sup> Once the patient begins to vomit, gut decontamination is unlikely to be beneficial. Although controversial, gastric lavage may be considered for patients presenting within 1 hour from ingestion.<sup>111</sup>

Ricin is not amenable to dialysis and there is no currently available antidote.<sup>16</sup> The major treatment goals for a patient with oral ricin poisoning are to improve perfusion by aggressive fluid resuscitation, vasopressor therapy, and replenishing electrolytes. Patients should also be monitored and treated for any evidence of myoglobinuria and renal failure. For inhalational exposure, general supportive treatment may include oxygen, bronchodilators, endotracheal intubation, and supplemental positive end-expiratory pressure as needed.

**Disposition and Prognosis.** In the setting of a credible threat or suspicion of ricin poisoning, all symptomatic patients should be admitted to the hospital. The clinical course after ingestion and inhalation typically progresses over 4 to 36 hours, and monitoring in an intensive care unit may be warranted. Patients who re-

**Box 4. Differential Diagnosis for Ricin Poisoned Patients Based on Route of Exposure****Ingestion and Gastrointestinal Illness\***

## Localized

## Chemical or Toxin

- Simple hydrocarbons
- Strong detergents
- Caustic agents (corrosives, acids, bases)
- Pharmaceuticals (eg, colchicines, salicylates, digoxin)
- Mushroom species (eg, *Boletes species*, *Lactarius species*)
- Diarrheic shellfish poisoning (okadaic acid)
- Plant species (eg, Pokeweed; *Phytolacca speces*, solanine-containing plants)

## Infectious†

- Enterotoxins of *Staphylococcus aureus*, *Bacillus cereus* (Type I), and *Clostridium perfringens*
- Anasikiasis*†
- Escherichia coli*
- Late presentation of enteric pathogens (eg, salmonella, shigella, cholera, *campylobacter jejuni*, *yersinia enterocolitica*)

**Multiorgan Dysfunction**

## Chemical

- Abrin (*Abrus precatorius*)
- Metals (eg, arsenic, mercury, copper, lead, cadmium, others)
- Certain mushroom species (eg, *Amanita phalloides*)
- Pharmaceuticals (eg, colchicine, antimetabolite cancer drugs)

**Infectious Agents Causing Sepsis**

\*Toxicity of ingested ricin is dose-dependent with small ingestions resulting in localized gastrointestinal tract signs and symptoms. Ingestion of larger amounts will result in these localized symptoms as well but may also progress to systemic poisoning such as hepatic and renal dysfunction.

†Agents that typically cause gastrointestinal tract manifestations within 1 to 6 hours of ingestion and is more consistent with expected presentation of ricin poisoning from ingestion. Other infectious foodborne agents typically have a delay from 8 to 72 hours before symptom onset and may be less likely depending on the situation.

**Inhalation and Respiratory Illness**

## Chemical or Toxin

- Irritant gases: ozone, chlorine, phosphine, phosgene, oxides of nitrogen
- Metal fume fever
- Polymer fume fever
- Particulate irritants: smoke, fumes, acid mists, dusts
- Paraquat
- Abrin

## Infectious

- Influenza
- Pneumonic plague
- Q fever
- Anthrax
- Inhalational tularemia
- Other bacterial or viral agents that cause a diffuse, non-localized pneumonic process

**Pulmonary Diseases**

- Chronic obstructive pulmonary disease obstruction exacerbation
- Asthma

main completely asymptomatic for 12 hours after oral or inhalational exposure to ricin are unlikely to develop toxicity and may be discharged to home with appropriate precautions.<sup>16,52</sup> Experimental animal evidence suggests a possibility of delayed respiratory symptoms at 20 to 24 hours after ricin inhalation<sup>77</sup>; thus, all discharged patients should be instructed to return immediately to the emergency department if symptoms develop. Recognition and treatment of ricin exposures may vary with age, other constitu-

tional factors, and underlying disease states; susceptibility factors are unknown (Figure 2).<sup>112,113</sup>

**Dermal.** After appropriate skin decontamination (Box 3) and counseling, asymptomatic patients with isolated dermal exposure can be discharged. The possibility of absorption through abraded or burned skin has not been investigated and these patients may be monitored for 12 hours for development of illness, for systemic absorption and subsequent delay in onset of illness is possible.

**CONCLUSION**

Recent threats of ricin release and procurement of ricin as a terrorist weapon highlight the need for clinicians and public health officials to be vigilant for illness suggestive of ricin exposure. Clinical manifestations of ricin poisoning will vary depending on the routes of exposure. In the setting of a credible threat, clinicians should consider ricin poisoning in patients presenting with gastrointestinal or respiratory tract illness, especially in the setting of progressively worsening symptoms and organ dys-

function. To facilitate early diagnosis and reduce further morbidity and mortality, poison control centers, public health and local law enforcement agencies should be notified of any known illness associated with ricin exposure or outbreak of illness consistent with ricin poisoning.

**Author Contributions:** Dr Audi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Financial Disclosures:** None reported.

**Funding/Support:** No outside or commercial funding source was provided for the development and completion of this manuscript.

**Disclaimer:** The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, the Agency for Toxic Substances, and Disease Registry. This article did receive clearance through the appropriate channels at the Centers for Disease Control and Prevention prior to submission.

**Acknowledgment:** We thank Carol Rubin, DVM, MPH, Chief Health Studies Branch, National Center for Environmental Health, CDC; Max Kiefer, MS CIH, Assistant Director for Emergency Preparedness, National Institute for Occupational Safety and Health, CDC; and Jerry Thomas, MD, Medical Toxicologist, Division of Laboratory Sciences, CDC.

#### REFERENCES

- Centers for Disease Prevention and Control. Investigation of a ricin-containing envelope at a postal facility—South Carolina, 2003. *MMWR Morb Mortal Wkly Rep.* 2003;52:1129-1131.
- Centers for Disease Control and Prevention. Recommendations of the CDC Strategic Planning Workgroup Biological and Chemical Terrorism: strategic plan for preparedness and response. *MMWR Morb Mortal Wkly Rep.* 2000;49(RR-4):1-14.
- Cope AC, Dee J, Cannan RK, et al. *Chemical Warfare Agents and Related Chemical Problems—Part I: Summary Technical Report of Division 9.* Washington, DC: National Defense Research Committee. 1945; 179-203.
- Parker DT, Parker AC, Ramachandran CK. *Joint Technical Data Source Book.* Vol 6. Part 3. US Dugway Proving Ground, Utah: Joint Contact Point Directorate. 1996;1-38. DGP No. DPGJCP-961007.
- Balint GA. Ricin: the toxic protein of castor oil seeds. *Toxicology.* 1974;2:77-102.
- Bradberry SM, Dickens KJ, Rice P, Griffiths GD, Vale JA. Ricin poisoning. *Toxicol Rev.* 2003;22:65-70.
- Bies C, Lehr CM, Woodley JF. Lectin-mediated drug targeting: history and applications. *Adv Drug Deliv Rev.* 2004;56:425-435.
- Cmiech HA, Morley M, Gee DJ. Immunocytochemical detection of ricin, I: preliminary immunofluorescence studies. *Histochem J.* 1985;17:859-866.
- Godal A, Fodstad O, Ingebrigtsen K, Pihl A. Pharmacological studies of ricin in mice and humans. *Cancer Chemother Pharmacol.* 1984;13:157-163.
- Lord JM, Gould J, Griffiths D, et al. Ricin: cytotoxicity, biosynthesis and use in immunoconjugates. *Prog Med Chem.* 1987;24:1-28.
- Lord JM, Roberts LM, Robertus JD. Ricin: structure, mode of action, and some current applications. *FASEB J.* 1994;8:201-208.
- Vitetta ES, Uhr JW. Immunotoxins: redirecting nature's poisons. *Cell.* 1985;41:653-654.
- Olsnes S. The history of ricin, abrin and related toxins. *Toxicol.* 2004;44:361-370.
- Brugsch HG. Toxic hazards: the castor bean. *N Engl J Med.* 1960;262:1039-1040.
- Burrows WD, Renner SE. Biological warfare agents as threats to potable water. *Environ Health Perspect.* 1999;107:975-984.
- Challoner KR, McCarron MM. Castor bean intoxication: review of reported cases. *Ann Emerg Med.* 1990;19:1177-1183.
- Scarpa A, Guerci A. Various uses of the castor oil plant (*Ricinus communis* L.): a review. *J Ethnopharmacol.* 1982;5:117-137.
- Eitzen E, Palvin J, Cieslak T, et al. *Medical Management of Biological Casualties Handbook.* eds 3rd ed. Fort Detrick, Frederick, Md: US Army Medical Research Institute of Infectious Diseases. 1998;101-106.
- Crompton R, Gall D. Georgi Markov: death in a pellet. *Med Leg J.* 1980;48:51-62.
- Knight B. Ricin—a potent homicidal poison. *BMJ.* 1979;1:350-351.
- Zilinskas RA. Iraq's biological weapons: the past as future? *JAMA.* 1997;278:418-424.
- Mayor S. UK doctors warned after ricin poison found in police raid. *BMJ.* 2003;326:126.
- Bale JM, Bhattachajee A, Croddy E, Pilch R. Ricin found in London: an al-Qa'ida connection? Monterey, Calif: Center for Nonproliferation Studies, Chemical and Biological Weapons Nonproliferation Program. January 23, 2003. Available at: <http://cns.mis.edu/pubs/reports/ricin.htm>. Accessed October 2004.
- Roy CJ, Hale M, Hartings JM, et al. Impact of inhalation exposure modality and particle size on the respiratory deposition of ricin in BALB/c mice. *Inhal Toxicol.* 2003;15:619-638.
- Doebler JA, Wiltshire ND, et al. The distribution of [<sup>125</sup>I] ricin in mice following aerosol inhalation exposure. *Toxicology.* 1995;98:137-149.
- Ishiguro M, Tomi M, Funatsu G, Funatsu M. Isolation and chemical properties of a ricin variant from castor bean. *Toxicol.* 1976;14:157-165.
- Morino H, Sakakibara R, Ishiguro M. The binding of ricin to its receptor is not required for the expression of its toxicity. *Biol Pharm Bull.* 1995;18:1770-1772.
- Day PJ, Pinheiro TJ, Roberts LM, Lord JM. Binding of ricin A-chain to negatively charged phospholipid vesicles leads to protein structural changes and destabilizes the lipid bilayer. *Biochemistry.* 2002;41:2836-2843.
- Olsnes S, Saltvedt E, Pihl A. Isolation and comparison of galactose-binding lectins from *Abrus precatorius* and *Ricinus communis*. *J Biol Chem.* 1974;249:803-810.
- Sandvig K, Olsnes S. Entry of the toxic proteins abrin, modeccin, ricin, and diphtheria toxin into cells, I: requirement for calcium. *J Biol Chem.* 1982;257:7495-7503.
- Sandvig K, Olsnes S. Entry of the toxic proteins abrin, modeccin, ricin, and diphtheria toxin into cells, II: effect of pH, metabolic inhibitors, and ionophores and evidence for toxin penetration from endocytotic vesicles. *J Biol Chem.* 1982;257:7504-7513.
- Sandvig K, van Deurs B. Entry of ricin and Shiga toxin into cells: molecular mechanisms and medical perspectives. *EMBO J.* 2000;19:5943-5950.
- Endo Y. Mechanism of action of ricin and related toxins on the inactivation of eukaryotic ribosomes. *Cancer Treat Res.* 1988;37:75-89.
- Lord MJ, Jolliffe NA, Marsden CJ, et al. Ricin: mechanisms of cytotoxicity. *Toxicol Rev.* 2003;22:53-64.
- Olsnes S, Pihl A. Treatment of abrin and ricin with  $\beta$ -mercaptoethanol—opposite effects on their toxicity in mice and their ability to inhibit protein synthesis in a cell-free system. *FEBS Lett.* 1972;28:48-50.
- Olsnes S, Refsnes K, Christensen TB, Pihl A. Studies on the structure and properties of the lectins from *Abrus precatorius* and *Ricinus communis*. *Biochim Biophys Acta.* 1975;405:1-10.
- Olsnes S, Sandvig K, Refsnes K, Pihl A. Rates of different steps involved in the inhibition of protein synthesis by the toxic lectins abrin and ricin. *J Biol Chem.* 1976;251:3985-3992.
- Flexner S. The histological changes produced by ricin and abrin intoxications. *J Exp Med.* 1897;2:197-216.
- Griffiths GD, Leek MD, Gee DJ. The toxic plant proteins ricin and abrin induce apoptotic changes in mammalian lymphoid tissues and intestine. *J Pathol.* 1987;151:221-229.
- Hughes JN, Lindsay CD, Griffiths GD. Morphology of ricin and abrin exposed endothelial cells is consistent with apoptotic cell death. *Hum Exp Toxicol.* 1996;15:443-451.
- Kumar O, Sugendran K, Vijayaraghavan R. Oxidative stress associated hepatic and renal toxicity induced by ricin in mice. *Toxicol.* 2003;41:333-338.
- Lombard S, Helmy ME, Pieroni G. Lipolytic activity of ricin from *Ricinus sanguineus* and *Ricinus communis* on neutral lipids. *Biochem J.* 2001;358:773-781.
- Pappenheimer AM Jr, Olsnes S, Harper AA. Lectins from *Abrus precatorius* and *Ricinus communis*, I: immunochemical relationships between toxins and agglutinins. *J Immunol.* 1974;113:835-841.
- Hegde R, Podder SK. Studies on the variants of the protein toxins ricin and abrin. *Eur J Biochem.* 1992;204:155-164.
- Morlon-Guyot J, Helmy M, Lombard-Frasca S, et al. Identification of the ricin lipase site and implication in cytotoxicity. *J Biol Chem.* 2003;278:17006-17011.
- Corwin AH. Toxic constituents of the castor bean. *J Med Pharm Chem.* 1961;4:483-490.
- Darby SM, Miller ML, Allen RO. Forensic determination of ricin and the alkaloid marker ricinine from castor bean extracts. *J Forensic Sci.* 2001;46:1033-1042.
- Ferraz AC, Pereira LF, Ribeiro RL, et al. Ricinine-elicited seizures: a novel chemical model of convulsive seizures. *Pharmacol Biochem Behav.* 2000;65:577-583.
- Ferraz AC, Anselmo-Franci JA, Perosa SR, et al. Amino acid and monoamine alterations in the cerebral cortex and hippocampus of mice submitted to ricinine-induced seizures. *Pharmacol Biochem Behav.* 2002;72:779-786.
- Waller GR, Tang MS, Scott MR, et al. Metabolism of ricinine in the castor plant. *Plant Physiol.* 1965;40:803-807.
- Klaim GJ, Jaeger JJ. *Castor Seed Poisoning in Humans: A Review: Technical Report # 453.* San Francisco, Calif: Letterman Army Institute of Research; January 1990.
- Rauber A, Heard J. Castor bean toxicity re-examined: a new perspective. *Vet Hum Toxicol.* 1985;27:498-502.
- Kopferschmitt J, Flesch F, Lugnier A, et al. Acute voluntary intoxication by ricin. *Hum Toxicol.* 1983;2:239-242.
- Ishiguro M, Mitarai M, Harada H, et al. Biochemical studies on oral toxicity of ricin, I: ricin administered orally can impair sugar absorption by rat small intestine. *Chem Pharm Bull (Tokyo).* 1983;31:3222-3227.
- Ishiguro M, Tanabe S, Matori Y, Sakakibara R. Biochemical studies on oral toxicity of ricin, IV: a fate of orally administered ricin in rats. *J Pharmacobiodyn.* 1992;15:147-156.
- Bispham WN. Report of cases of poisoning by the fruit of *Ricinus communis*. *Am J Med Sci.* 1903;12:319-321.
- Kinamore PA, Jaeger RW, de Castro FJ. Abrus and ricinus ingestion: management of three cases. *Clin Toxicol.* 1980;17:401-405.
- Koch LA, Caplan J. Castor bean poisoning. *AJDC.* 1942;64:485-486.

59. Malizia E, Sarcinelli L, Andreucci G. Ricinus poisoning: a familiar epidemic. *Acta Pharmacol Toxicol (Copenh)*. 1977;41(suppl 2):351-361.
60. Reed RP. Castor oil seed poisoning: a concern for children. *Med J Aust*. 1998;168:423-424.
61. Satpathy R, Das BB. Accidental poisoning in childhood. *J Indian Med Assoc*. 1979;73:190-192.
62. Palatnick W, Tenenbein M. Hepatotoxicity from castor bean ingestion in a child. *J Toxicol Clin Toxicol*. 2000;38:67-69.
63. Wedin GP, Neal JS, Everson GW, Krenzelok EP. Castor bean poisoning. *Am J Emerg Med*. 1986;4:259-261.
64. Furbue B, Wermuth M. Life-threatening plant poisoning. *Crit Care Clin*. 1997;13:849-888.
65. Meldrum WP. Poisoning by castor oil seeds. *BMJ*. 1900;8:317.
66. Sekine I, Kawase Y, Nishimori I, et al. Pathological study on mucosal changes in small intestine of rat by oral administration of ricin, I: microscopical observation. *Acta Pathol Jpn*. 1986;36:1205-1212.
67. Fodstad O, Olsnes S, Pihl A. Toxicity, distribution and elimination of the cancerostatic lectins abrin and ricin after parenteral injection into mice. *Br J Cancer*. 1976;34:418-425.
68. Fodstad O, Johannessen JV, Schjervan L, Pihl A. Toxicity of abrin and ricin in mice and dogs. *J Toxicol Environ Health*. 1979;5:1073-1084.
69. Blakey DC, Skilleter DN, Price RJ, et al. Comparison of the pharmacokinetics and hepatotoxic effects of saporin and ricin A-chain immunotoxins on murine liver parenchymal cells. *Cancer Res*. 1988;48:7072-7078.
70. Ramsden CS, Drayson MT, Bell EB. The toxicity, distribution and excretion of ricin holotoxin in rats. *Toxicology*. 1989;55:161-171.
71. Fine DR, Shepherd HA, Griffiths GD, Green M. Sub-lethal poisoning by self-injection with ricin. *Med Sci Law*. 1992;32:70-72.
72. Targosz D, Winnik L, Szkolnicka B. Suicidal poisoning with castor bean (*ricinus communis*) extract injected subcutaneously: case report [abstract]. *J Toxicol Clin Toxicol*. 2002;40:398.
73. Leek MD, Griffiths GD, Green MA. Intestinal pathology following intramuscular ricin poisoning. *J Pathol*. 1989;159:329-334.
74. Skilleter DN, Paine AJ, Stirpe F. A comparison of the accumulation of ricin by hepatic parenchymal and non-parenchymal cells and its inhibition of protein synthesis. *Biochim Biophys Acta*. 1981;677:495-500.
75. Bingen A, Creppy EE, Gut JP, et al. The Kupffer cell is the first target in ricin-induced hepatitis. *J Submicrosc Cytol*. 1987;19:247-256.
76. Griffiths GD, Rice P, Allenby AC, et al. Inhalation toxicology and histopathology of ricin and abrin toxins. *Inhal Toxicol*. 1995;7:269-288.
77. Wilhelmsen CL, Pitt ML. Lesions of acute inhaled lethal ricin intoxication in rhesus monkeys. *Vet Pathol*. 1996;33:296-302.
78. Brown RF, White DE. Ultrastructure of rat lung following inhalation of ricin aerosol. *Int J Exp Pathol*. 1997;78:267-276.
79. Griffiths GD, Lindsay CD, Upshall DG. Examination of the toxicity of several protein toxins of plant origin using bovine pulmonary endothelial cells. *Toxicology*. 1994;90:11-27.
80. Figley KD, Rawling FF. Castor bean: an industrial hazard as a contaminant of green coffee dust and used burlap bags. *J Allergy*. 1950;21:545-553.
81. Figley KD, Elrod RH. Endemic asthma due to castor bean dust. *JAMA*. 1928;90:79-82.
82. Kathern RI, Price H, Rogers JC. Air-borne castor-bean pomace allergy: a new solution to an old problem. *AMA Arch Industr Health*. 1959;19:487-489.
83. Kemeny DM, Frankland AW, Fahkri ZI, Trull AK. Allergy to castor bean in the Sudan: measurement of serum IgE and specific IgE antibodies. *Clin Allergy*. 1981;11:463-471.
84. Ordman D. An outbreak of bronchial asthma in South Africa, affecting more than 200 persons, caused by castor bean dust from an oil-processing factory. *Int Arch Allergy Appl Immunol*. 1955;7:10-24.
85. Layton LL, Yamanaka E, Green TW. Multiple allergies to the pollen and seed antigens of *Ricinus communis* (castor bean). *J Allergy*. 1962;33:232-235.
86. Metz G, Bocher D, Metz J. IgE-mediated allergy to castor bean dust in a landscape gardener. *Contact Dermatitis*. 2001;44:367.
87. Thorpe SC, Murdoch RD, Kemeny DM. The effect of the castor bean toxin, ricin, on rat IgE and IgG responses. *Immunology*. 1989;68:307-311.
88. Thorpe SC, Kemeny DM, Panzani R, Lessof MH. Allergy to castor bean, I: its relationship to sensitization to common inhalant allergens (atopy). *J Allergy Clin Immunol*. 1988;82:62-66.
89. Thorpe SC, Kemeny DM, Panzani RC, McGurl B, Lord M. Allergy to castor bean, II: identification of the major allergens in castor bean seeds. *J Allergy Clin Immunol*. 1988;82:67-72.
90. Kanerva L, Estlander T, Jolanki R. Long-lasting contact urticaria from castor bean. *J Am Acad Dermatol*. 1990;23:351-355.
91. Grant WM, Schuman JS. Toxicology of the eye. *Effects on the Eyes and Visual System From Chemicals, Drugs, Metals and Minerals, Plants, Toxins and Venoms*. Springfield: Ill: Charles C Thomas Publishers. 4th ed. 1993;246, 888.
92. Griffiths GD, Newman H, Gee DJ. Identification and quantification of ricin toxin in animal tissues using ELISA. *J Forensic Sci Soc*. 1986;26:349-358.
93. Griffiths GD, Newman HV, Gee DJ. Immunocytochemical detection of ricin, II: further studies using the immunoperoxidase method. *Histochem J*. 1986;18:189-195.
94. Leith AG, Griffiths GD, Green MA. Quantification of ricin toxin using a highly sensitive avidin/biotin enzyme-linked immunosorbent assay. *J Forensic Sci Soc*. 1988;28:227-236.
95. Poli MA, Rivera VR, Hewetson JF, Merrill GA. Detection of ricin by colorimetric and chemiluminescence ELISA. *Toxicon*. 1994;32:1371-1377.
96. Shyu RH, Shyu HF, Liu HW, Tang SS. Colloidal gold-based immunochromatographic assay for detection of ricin. *Toxicon*. 2002;40:255-258.
97. Shyu HF, Chiao DJ, Liu HW, Tang SS. Monoclonal antibody-based enzyme immunoassay for detection of ricin. *Hybrid Hybrids*. 2002;21:69-73.
98. Godal A, Olsnes S, Pihl A. Radioimmunoassays of abrin and ricin in blood. *J Toxicol Environ Health*. 1981;8:409-417.
99. Johnson RC, Lemire SW, Woolfitt AR, et al. Quantification of ricinine in rat and human urine: a biomarker for ricin exposure. *J Anal Toxicol*. 2005;29:149-155.
100. Poli MA, Rivera VR, Pitt ML, Vogel P. Aerosolized specific antibody protects mice from lung injury associated with aerosolized ricin exposure. *Toxicon*. 1996;34:1037-1044.
101. Smallshaw JE, Richardson JA, Pincus S, Schindler J, Vitetta ES. Preclinical toxicity and efficacy testing of RiVax, a recombinant protein vaccine against ricin. *Vaccine*. 2005;23:4775-4784.
102. Vogel P, Rivera VR, Pitt ML, Poli MA. Comparison of the pulmonary distribution and efficacy of antibodies given to mice by intratracheal instillation or aerosol inhalation. *Lab Anim Sci*. 1996;46:516-523.
103. Houston LL. Protection of mice from ricin poisoning by treatment with antibodies directed against ricin. *J Toxicol Clin Toxicol*. 1982;19:385-389.
104. Kende M, Yan C, Hewetson J, et al. Oral immunization of mice with ricin toxoid vaccine encapsulated in polymeric microspheres against aerosol challenge. *Vaccine*. 2002;20:1681-1691.
105. Griffiths GD, Phillips GJ, Bailey SC. Comparison of the quality of protection elicited by toxoid and peptide liposomal vaccine formulations against ricin as assessed by markers of inflammation. *Vaccine*. 1999;17:2562-2568.
106. Smallshaw JE, Firan A, Fulmer JR, et al. A novel recombinant vaccine which protects mice against ricin intoxication. *Vaccine*. 2002;20:3422-3427.
107. Griffiths GD, Lindsay CD, Allenby AC, et al. Protection against inhalation toxicity of ricin and abrin by immunisation. *Hum Exp Toxicol*. 1995;14:155-164.
108. Ricin emergency response card Web page. Available at: <http://www.bt.cdc.gov/agent/ricin/erc9009-86-3pr.asp>. Accessed January 2004. Atlanta, Ga: National Institute for Occupational Safety and Health.
109. Wannemacher RW, Dinterman RE, Thompson WL, Schmidt MO, Burrows WD. *Treatment for Removal of Biotoxins from Drinking Water*. Fort Detrick, Md: US Army Biomedical Research and Development Laboratory; 1993. No. TR9120, AD 275958.
110. Chyka PA, Seger D. Position statement: single-dose activated charcoal: American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1997;35:721-741.
111. Vale JA. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement: gastric lavage. *J Toxicol Clin Toxicol*. 1997;35:711-719.
112. Franz DR, Jahrling PB, McClain DJ, et al. Clinical recognition and management of patients exposed to biological warfare agents. *Clin Lab Med*. 2001;21:435-473.
113. Centers for Disease Control and Prevention (CDC). Recognition of illness associated with exposure to chemical agents—United States, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52:938-940.