Chapter 31

STAPHYLOCOCCAL ENTEROTOXIN B AND RELATED PYROGENIC TOXINS

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INTRODUCTION

Staphylococcal enterotoxin B (SEB) is one of seven enterotoxins produced by strains of *Staphylococcus aureus*. SEB, the best understood of the staphylococcal enterotoxins, can be regarded as the "type" enterotoxin. Staphylococcal enterotoxins, toxic shock syndrome toxin–1 (TSST-1), and certain other bacterial products (such as streptococcal pyrogenic exotoxins [SPE]) and viral products (which are not discussed in this chapter) are commonly referred to as *superantigens* because of their profound effects on the immune system. Minute concentrations of superantigens can activate the immune system receptors because they bind with strong avidity to T-cell antigen receptors and class II molecules of the major histocompatibility complex (MHC).

The staphylococcal enterotoxins are the most frequent cause of food poisoning. However, more severe physiological consequences, such as a life-threatening toxic shock–like syndrome, may result from exposure to these toxins through a nonenteric route. Although high-dose exposures may well cause fatalities, it is the *incapacitating* consequences of inhalational exposure to agents such as SEB on the battlefield that are of most concern in the context of biological defense.

During the 1960s, when the United States had an offensive biological warfare program, SEB (then code-named PG) was studied extensively as a biological incapacitant. This toxin was especially attractive as a biological agent because much lower quantities were needed to produce the desired effect than were required with synthetic chemicals. The dose that is incapacitating for 50% of the human population exposed (also called the effective dose [ED_{50}]) was found to be 0.0004 µg/kg, and the dose that is lethal for 50% of the human population exposed (LD_{50}) was estimated to be approximately 0.02 µg/kg, both by the inhalational route.[1]

DESCRIPTION OF THE AGENT

The staphylococcal and streptococcal toxins with superantigen-like properties are 23- to 29-kilodalton (kd) proteins (referred to here as pyrogenic toxins) that can be categorized into three distinct amino acid–sequence homology groups[2]:

1. The staphylococcal enterotoxin serotypes SEA, SED, and SEE are closely related; they form the first homology group.
2. Staphylococcal enterotoxin serotypes SEB, SEC1, SEC2, SEC3, and the streptococcal pyrogenic exotoxins A and C (SPE-A and SPE-C) form the second homology group.
3. The third homology group comprises toxic shock syndrome toxin (TSST-1) and SPE-B, which share key amino acid residues with the other toxins but exhibit only weak sequence homology overall. However, data from X-ray crystallography of SEB[2] and TSST-1[3,4] indicate that these representatives of the two groups have considerable similarities in their three-dimensional structures.

The pyrogenic toxins bind to MHC class II molecules and this complex, in turn, stimulates T cells.[5–8] In contrast, MHC-independent binding induces T-cell anergy. It is likely that all pyrogenic toxins share a common mode for binding MHC class II molecules, with additional stabilizing interactions that are unique to each toxin.[9] A second, zinc-dependent molecular binding mode for SEA and SEE increases T-cell signaling and may account for the greater toxicities of these toxins. In conventional antigen-specific responses, the cluster of differentiation 4 (CD4) molecule stabilizes interactions between T-cell antigen receptors and MHC class II molecules on antigen presenting cells. The pyrogenic toxins may mimic CD4 binding[10] and, by so doing, stimulate large numbers of T cells in a manner independent of antigen recognition.

In addition, each superantigen stimulates T cells bearing characteristically distinct variable domain-β(Vβ) subsets of antigen receptors (Table 31-1). It is thought that a massive release of cytokines (such as interferon gamma, interleukin-6, and tumor necrosis factor–alpha) is responsible for the systemic effects of the toxins.[11] In contrast, the gastrointestinal illness especially prominent after ingestion of staphylococcal enterotoxins is associated with histamine and leukotriene release from mast cells.[12] Endotoxin from Gram-negative bacteria may act in concert with pyrogenic toxins to greatly amplify lethality. For example, mice are ordinarily unaffected by SEB and related toxins, but they become susceptible to doses in nanogram amounts when coadministered with nonlethal amounts of endotoxin.[11]

TABLE 31-1

HUMAN T-LYMPHOCYTE RESPONSE TO BACTERIAL SUPERANTIGENS

Superantigen (Pyrogenic Toxin)	T-Cell Receptor Vβ Used by Responding Lymphocytes[*]
SEA	1.1, 5.3, 6.3, 6.4, 7.3, 7.4, 9.1
SEB	3, 12, 14, 15, 17, 20
SEC1	12
SEC2	12, 13.1, 13.2, 14, 15, 17, 20
SEC3	5, 12
SED	5, 12
SEE	5.1, 6.1, 6.2, 6.3, 8.1, 18
TSST-1	2

[*]These T cells are the predominant phenotypes stimulated by each toxin, independent of the donor.
Vβ: variable domain-β
SE: staphylococcal enterotoxin
TSST-1: toxic shock syndrome toxin 1
Data sources: (1) Kappler J, Kotzin B, Herron L, et al. Vβ-specific stimulation of human T cells by staphylococcal toxins. *Science*. 1989;244:811–813. (2) Marrack P, Kappler J. The staphylococcal enterotoxins and their relatives. *Science*. 1990;248:705–711. (3) Champagne E, Huchenq A, Sevin J, Casternan N, Rubin B. An alternative method for T-cell receptor repertoire analysis: Clustering of human V-beta subfamilies selected in responses to staphylococcal enterotoxins B and E. *Mol Immunol*. 1993; 30(10):877–886.

Primates, including humans, are most sensitive to pyrogenic toxins because the binding affinity of their MHC class II molecules is greater. Lymphocyte responses of chimpanzees and humans are very similar, while rhesus monkeys are more sensitive to toxin stimulation. These differences in primate lymphocyte responses appear to be more dependent on the T cell than the cells presenting the MHC class II receptor.[13] However, pyrogenic toxins do vary in their affinity toward different MHC class II isotypes and alleles. Therefore, it is possible that MHC polymorphisms within the human population may also contribute to individual differences in susceptibility to the toxic effects of the pyrogenic toxins. In-

bred mice differing in MHC alleles, for example, have widely varying sensitivities to the staphylococcal enterotoxins.

Although little information is available concerning environmental reservoirs, domestic infections of rodents and other animals with strains that produce TSST-1 and the staphylococcal enterotoxins have been demonstrated.[14,15] Both ovine- and bovine-specific staphylococcal toxins, which are associated with mastitis, are almost identical to TSST-1 in their amino acid sequence.[16] Pyrogenic toxin–producing strains of *Staphylococcus aureus* and group A streptococcus are appearing with increasing frequency in clinical isolates. Approximately 50% of nonmenstrual toxic shock syndrome cases are linked to TSST-1, while the remaining cases are attributable to enterotoxins, with SEB predominating.[17] Kawasaki disease and some forms of arthritis have been causally linked to organisms producing streptococcal pyrogenic exotoxins, SEA, and TSST-1, although this is still controversial.[18] In addition, a severe form of streptococcal pneumonia, with accompanying toxic shock syndrome–like symptoms is caused by SPE-producing bacterial strains.[19] It is of interest also to note that the majority of group A streptococcal cultures produce pyrogenic exotoxins.

Most of the pyrogenic toxins are encoded by mobile genetic elements. SPE-A, SPE-C, SEA, and SEE are all phage-borne, while SED is plasmid-encoded. Insufficient data are available to clearly define the nature of SEB and TSST-1 genetic elements.[20] Because there is little evidence of genetic drift, it has been suggested that the majority of staphylococcal and streptococcal toxic shock–like syndrome bacterial isolates have each descended from single clones.[21] Production of the various staphylococcal pyrogenic toxins is dependent on the phase of cell growth cycle, environmental pH, and glucose concentration. Transcriptional control of TSST-1, SEB, SEC, and SED is mediated through the accessory gene regulator (*agr*) locus,[20] while SEA expression appears to be independent of *agr*. Strains that are *agr* negative are generally low toxin producers. However, there are also considerable differences in production levels between *agr* positive isolates.

PATHOGENESIS

Rhesus macaques (*Macaca mulatta*) have been used extensively as a model for lethal inhaled intoxication of SEB. Efforts to develop lethal aerosolized SEB animal models in rabbits and endotoxin-primed mice are ongoing. The following pre-

viously unpublished information is derived from a study of dose ranging during the development of a sublethal model conducted by one of the authors of this chapter (C.L.W.) in 1994 at U.S. Army Medical Research Institute of Infectious Diseases, Fort
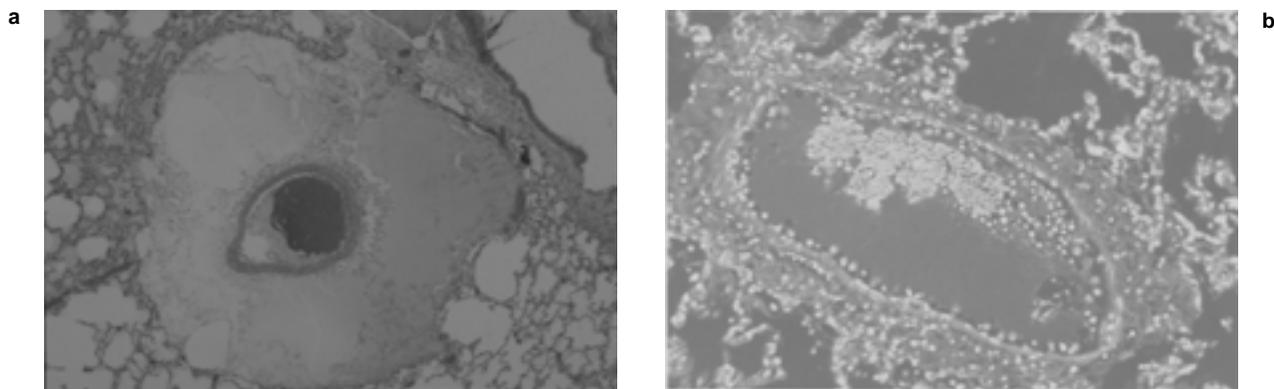
Fig. 31-1. Lung of a rhesus monkey that died of inhaled staphylococcal enterotoxin B (SEB) intoxication. (**a**) Marked perivascular interstitial edema and focal loss of bronchial epithelium can be seen (hematoxylin-eosin stain, original magnification x 10). (**b**) The intravascular mononuclear cells include lymphocytes, lymphoblasts, monocytes, and mononuclear phagocytes (hematoxylin-eosin stain, original magnification x 50).

Detrick, Frederick, Maryland. Similar information, from another study using different monkeys, was published in 1995 from the same laboratory.[22]

In recent studies, young and mature adult male and female rhesus monkeys developed signs of SEB intoxication after being exposed to a lethal dose of aerosolized SEB for 10 minutes in a modified Henderson head-only aerosol exposure chamber.[23] These animals demonstrated no detectable anti-SEB antibody prior to exposure.

Generally, SEB-intoxicated monkeys developed gastrointestinal signs within 24 hours after the exposure. Clinical signs were mastication, anorexia, emesis, and diarrhea. Following mild, brief, self-limiting gastrointestinal signs, the monkeys had a variable period of up to 40 hours of clinical improvement. At approximately 48 hours after the exposure, intoxicated monkeys generally had an abrupt onset of rapidly progressive lethargy, dyspnea, and facial pallor, culminating in death or euthanasia within 4 hours of onset.

At postmortem examination, most monkeys had similar gross pulmonary lesions. Lungs were diffusely heavy and wet, with multifocal petechial hemorrhages and areas of atelectasis. Clear, serous-to-white, frothy fluid often drained freely from the laryngeal orifice. The small and large intestines frequently had petechial hemorrhages and mucosal erosions. Typically, monkeys had mildly swollen lymph nodes, with moist and bulging cut surfaces.

Most monkeys had similar microscopic pulmonary lesions (Figure 31-1). The most obvious lesion was marked multifocal-to-coalescing interstitial pulmonary edema involving multiple lung lobes. Peribronchovascular connective tissue spaces were distended by pale, eosinophilic, homogeneous, proteinaceous material (edema);
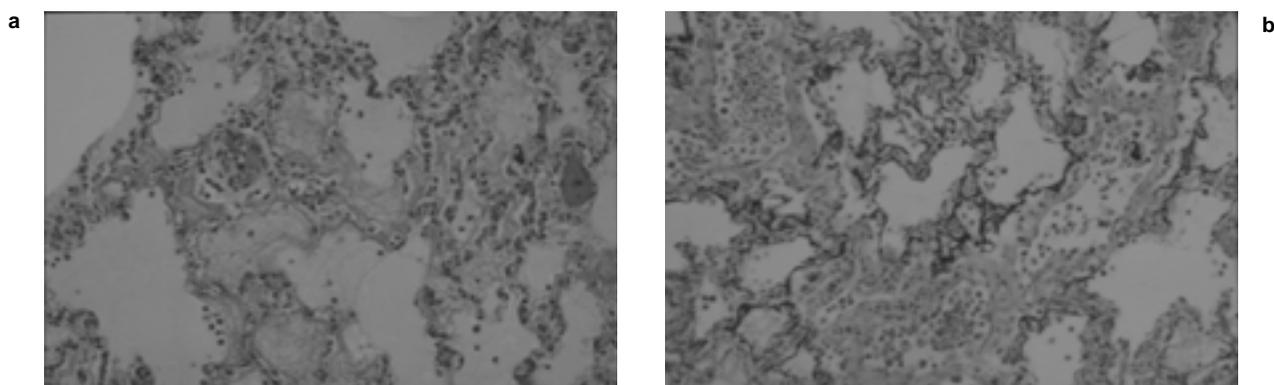

Fig. 31-2. Lung of a rhesus monkey that died of inhaled staphylococcal enterotoxin B (SEB) intoxication. (**a**) Intraalveolar fibrin deposition and hyaline membrane formation can be seen (hematoxylin-eosin stain, original magnification x 50). (**b**) Intraalveolar deposition of polymerized fibrin can be seen (phosphotungstic acid hematoxylin stain, original magnification x 50).

variably accompanied by entrapped, beaded fibrillar (fibrin) strands; and extravasated erythrocytes, neutrophils, macrophages, and small and large lymphocytes. Perivascular lymphatics were generally distended by similar eosinophilic material and inflammatory cells. Most monkeys had intravascular circulating and marginated neutrophils, monocytes, mononuclear phagocytes, and lymphocytes, including large lymphocytes with prominent nucleoli (lymphoblasts), some in mitosis. Extravascular extension of these cell types was interpreted as exocytosis/chemotaxis.

Loss of airway epithelium was inconsistent. Some monkeys had multifocal, asymmetric denudation of bronchial epithelium, with near total loss of the bronchiolar epithelium. Former bronchioles were recognized only by their smooth-muscle walls. Scant bronchial intraluminal exudate consisted of mucoid material, neutrophils, macrophages, and sloughed, necrotic cells.

A common finding was the combination of multifocal alveolar flooding and acute purulent alveolitis. Alveolar septa were distended by congested alveolar capillaries. Alveolar spaces were filled with eosinophilic, pale, homogeneous material (edema); with embedded, more deeply eosinophilic, beaded fibrillar strands (fibrin); or with condensed, eosinophilic, curvilinear deposits hugging the alveolar septal contours (hyaline membranes) (Figure 31-2). A variably severe, intraalveolar, cellular infiltrate of neutrophils, eosinophils, small lymphocytes, large lymphocytes (lymphoblasts), erythrocytes, and alveolar macrophages filled the alveolar spaces. Replicate pulmonary microsections stained with phosphotungstic acid–hematoxylin demonstrated alveolar fibrin deposition. Replicate microsections stained with Giemsa revealed scarce, sparsely granulated connective tissue mast cells.

In the upper respiratory tract, the tracheal and bronchial lamina propria was thickened by clear space or pale, eosinophilic, homogeneous material (edema); and neutrophils, small and large lymphocytes, and (possibly preexisting) plasma cells. The edema and cellular infiltrate extended transtracheally into the mediastinum, with moderate-to-marked mediastinal lymphangiectasia.

Lymphoid tissues of the respiratory tract had depletion of B-cell dependent areas and hyperplasia of T-cell dependent areas. The bronchus-associated lymphoid tissue (BALT) in some of the monkeys had follicular lymphocytic depletion. Most monkeys' mediastinal lymph nodes had subcapsular and medullary sinus edema and histiocytosis and paracortical lymphoid hyperplasia, characterized by numerous, closely packed, small lymphocytes, with interspersed macrophages bearing tingible bodies and large lymphocytes having prominent nucleoli (lymphoblasts) (Figure 31-3). There were scattered mitoses, including atypical mitoses. Cortical follicles had small, solid centers, or had hypocellular, hyalinized (depleted) centers.

Microscopic changes of lymphoid tissues elsewhere in the body mirrored changes in the respiratory mucosal lymphoid tissue. Mesenteric, axillary, inguinal, and retropharyngeal lymph nodes had sinus edema and his-
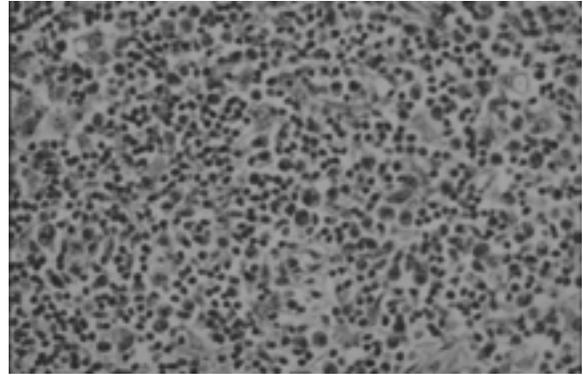

Fig. 31-3. Mediastinal lymph node of a rhesus monkey that died of inhaled staphylococcal enterotoxin B (SEB) intoxication. Paracortical lymphoproliferation with lymphoblasts can be seen (hematoxylin-eosin stain, original magnification x 100).

tiocytosis, paracortical lymphocytic and lymphoblastic hyperplasia, and unstimulated or depleted follicular centers. Also depleted were follicular germinal centers of gut-associated lymphoid tissue (GALT). Splenic T-cell dependent periarteriolar sheath zones were hypercellular, populated by a mix of small and large lymphocytes and macrophages, whereas B-cell dependent follicular areas were not recognized. Several monkeys had marked diffuse depletion of cortical thymocytes, with a "starry sky" appearance attributed to the presence of numerous thymic macrophages bearing tingible bodies.

Many monkeys had a mild, erosive enterocolitis, with slight multifocal, superficial mucosal loss, and with numerous lamina proprial macrophages bearing engulfed cellular debris. Crypt enterocytes had a high nuclear-to-cytoplasmic ratio and numerous mitoses. The crypt epi-
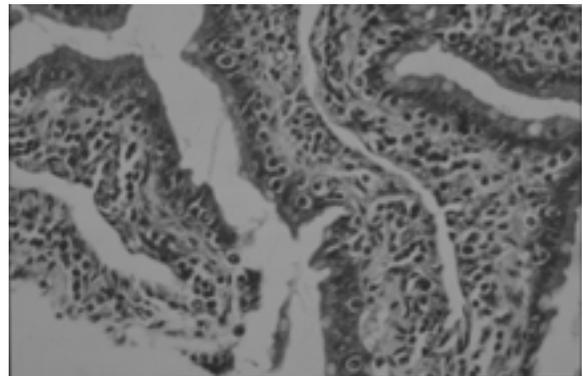

Fig. 31-4. Small intestine of a rhesus monkey that died of inhaled staphylococcal enterotoxin B (SEB) intoxication. Intraepithelial lymphoblastic leukocytes can be seen (hematoxylin-eosin stain, original magnification x 100).

thelium had a conspicuous population of large, mono-nuclear, intraepithelial leukocytes interpreted as lympho-blasts (Figure 31-4). Some monkeys' colons contained many small crypt abscesses.

Generalized vascular changes in most monkeys were congestion; swollen endothelial cells, with many intravas-cular large lymphocytes or lymphoblasts; and inconsis-tent widening of perivascular connective tissue spaces (by edema). Hepatic lesions were portal infiltrates of lym-phocytes, lymphoblasts, macrophages, and occasional neutrophils. The choroid plexus was slightly thickened (by edema).

True inhaled SEB pathogenesis studies, in which monkeys are killed and necropsied at sequen-tial times after the exposure, have not been con-ducted in recent years. To the best of our knowl-edge, there are no recently published reports of SEB pathogenesis studies in monkeys in the open literature.

Inhaled SEB appears to be a potent stimulant of the immune system of rhesus monkeys. Following inhalational exposure, there was microscopic lymphoproliferation of T-cell dependent areas of the lymphoid system. Recent immunohistochemical analysis of the large lymphocytes present in the pulmonary vasculature of rhesus monkeys lethally intoxicated with aerosolized SEB identified them as T cells, using anti-CD3 antibody.[22]

CLINICAL DISEASE

The clinical documentation of toxic shock syn-drome provides perhaps the most comprehensive source of information on the pathology of pyrogenic toxin exposure. To meet the strict Centers for Dis-ease Control criteria for toxic shock syndrome,[24] negative (except for *S aureus*) cultures of the blood, throat, or cerebrospinal fluid should be obtained; negative serologic tests for Rocky Mountain spot-ted fever, leptospirosis, and measles should also be obtained. Most of the pyrogenic toxins produce the same signs and symptoms as toxic shock syndrome: a rapid drop in blood pressure, elevated tempera-ture, and multiple organ failure. However, the res-piratory route of exposure to toxins may involve some unique mechanisms. The profound hypoten-sion characteristic of toxic shock syndrome is not observed, and respiratory involvement is rapid. Fever, prominent after aerosol exposure, is gener-ally not observed in cases of SEB ingestion.

A previously unpublished report from the labo-ratory of one of the authors of this chapter (S.S.) documents an accidental laboratory inhalational exposure of nine laboratory workers to SEB, and best exemplifies the clinical disease. At least one and perhaps two other workers were in the building at the time of the accident. They were examined but remained completely asymptomatic; they might not have been exposed. These additional workers are not included in this report; the nine mentioned are those who are known to have been exposed (be-cause they became ill).

This report describes a severely incapacitating illness of rapid onset (3–4 h) but modest duration (3–4 d). The degree of illness can be categorized as follows: three of the nine patients were seriously ill, and one of these three was profoundly ill; two of nine were moderately ill; and four of nine were mildly ill.

Fever and Myalgia

Fever was prominent in all nine of those exposed. Eight of the individuals experienced at least one shaking chill that heralded the onset of illness. Using the morning peak level of SEB aerosol generation in the laboratory as the most likely time of exposure, onset of fever occurred from 8 to 20 hours after the initial exposure, with a mean time of onset of 12.4 ± 3.9 (standard deviation) hours. Dura-tion of fever was from 12 to 76 hours after onset, with a mean duration of 50 ± 22.3 hours. Fever reached as high as 106°F acutely.

Myalgias were often associated with the initial fever. Onset of myalgia was from 8 to 20 hours, with a mean onset of 13 ± 5 hours. Duration of myalgia was from 4 to 44 hours, and the mean duration was 16 ± 15 hours.

Respiratory Signs and Symptoms

All nine patients were admitted to the hospital with a generally nonproductive cough. Onset of respiratory symptoms was 10.4 ± 5.4 hours, and duration was 92 ± 41 hours. Five of the nine patients had inspiratory rales with dyspnea. The three most seriously compromised patients had dyspnea, moist inspiratory and expiratory rales, and orthopnea; these signs gradually cleared. One of these three patients had profound dyspnea for the first 12 hours, which moderated to exertional dyspnea and rales that persisted for 10 days.

Chest radiographs taken on admission showed, in the three patients with inspiratory rales, densities compat-ible with "patches of pulmonary edema" and Kerley lines suggesting interstitial edema. During recovery, discoid atelectasis was noted. Moderate compromise of the res-piratory system was often accompanied by radiographic evidence of peribronchial accentuation or "cuffing." The three mildly ill patients had normal radiographs.

The one profoundly ill patient had severe pulmonary compromise and profound dyspnea, and received only slight relief when treated with an aminophylline suppository. Moderately intense chest pain, of a sub-sternal pleuritic type, occurred in seven of the nine

individuals. Onset of chest pain was 12 ± 6.5 hours; duration ranged from 4 to 84 hours, with a mean duration of 23 ± 27 hours.

Headache

Eight of the nine patients experienced headache. Onset ranged from 4 to 36 hours, and the mean time of onset was 13.3 ± 10 hours. Duration ranged from 8 to 60 hours, with a mean duration of 30.6 ± 19 hours. The headaches ranged from severe to mild, but usually were mild by the second hospital day. Five individuals' headache responded to Darvon (propoxyphene hydrochloride, manufactured by Eli Lilly and Company, Indianapolis, Indiana) or codeine.

Gastrointestinal Symptoms

Gastrointestinal symptoms occurred in most of the individuals: nausea and anorexia in six and vomiting in four. The onset of nausea ranged from 8 to 24 hours, with a mean onset of 17 ± 6.3 hours. Duration ranged from 4 to 20 hours, with a mean of 9 ± 5.5 hours. Onset of anorexia ranged from 8 to 24 hours, with a mean onset of 18.5 ± 5.6 hours. Duration of anorexia ranged from 4 to 136 hours, and the mean duration was 44.5 ± 45 hours. Vomiting occurred in four patients and sometimes occurred after prolonged paroxysms of coughing. The range of onset of vomiting was 8 to 20 hours, with a mean time to onset of 14 ± 5.1 hours. Duration was not prolonged and usually consisted of one episode. Compazine (prochlorperazine, manufactured by SmithKline Beecham Pharmaceuticals, Philadelphia, Pennsylvania) and Benadryl were employed successfully.

Only one individual demonstrated hepatomegaly and bile in the urine, although another patient also demonstrated mildly elevated liver function tests. (The liver function tests on this last patient remained elevated for years, but it is unclear whether this is actually a sequela of this illness. In addition, this individual had previous exposures to staphylococcal enterotoxins while working at a different laboratory.) No diarrhea was reported in any of the exposed individuals.

Other Signs and Symptoms

All patients who experienced chest pain had normal electrocardiograms. Throughout the illness, all were normotensive. Vomiting was of relatively brief duration and no patients, including those vomiting, required intravenous fluid administration. Pulse rate, when elevated, paralleled temperature elevation.

Leukocytosis was observed in most patients 12 to 24 hours after exposure to the toxin.

None of these individuals experienced conjunctivitis, although one individual later remembered that his eyes had "burned" during the believed time of exposure.

DETECTION AND DIAGNOSIS

The staphylococcal enterotoxins are moderately stable proteins; therefore, immunological evaluation should be possible on samples collected in either deployed or fixed medical treatment facilities. Immunoassays can detect picogram quantities of toxins in environmental samples. For comparison, 440 pg/mL was reported as the mean concentration of TSST-1 in human sera from patients with toxic shock syndrome.[25] Anti-TSST-1 antibody titers are either suppressed or depleted in patients with toxic shock syndrome[26,27] and the levels only recover during convalescence. In addition, most normal human serum samples contain detectable levels of antibody reacting with several different bacterial pyrogenic toxins, including SEB. Therefore, serum antibody titers are of little diagnostic value. If actual bacterial involvement is suspected, and if cultures can be obtained, the detection of extremely minute quantities of potentially toxigenic strains is possible by using (1) polymerase chain reaction (PCR) amplification and (2) toxin gene–specific oligonucleotide primers. The results from both methods are rapid, allowing quantitative or qualitative measurements in less than 24 hours.

Finally, for at least 12 to 24 hours after the exposure, toxins should be identifiable in nasal swabs from individuals exposed to a respirable aerosol. This may be the best approach to early diagnosis on the battlefield.

MEDICAL MANAGEMENT

Supportive therapy seems to have been adequate care in the nine patients described above with mild, accidental, respiratory exposure to aerosolized SEB. Symptoms of fever, muscle aches, and arthralgias may respond to cool compresses, fluids, rest, and judicious use of acetaminophen or aspirin. For nausea, vomiting, and anorexia, symptomatic therapy should be considered. Antihistamines (eg, diphenhydramine) and phenothiazine derivatives (eg, prochlorperazine) were used parenterally or as suppositories. The success of these drugs in controlling nausea may have been augmented by the relatively short duration of nausea and vomiting induced by aerosolized SEB. Because of the brevity of vomiting episodes, fluid replacement was not considered or required in the series dis-

cussed. However, in the event of prolonged vomiting resulting in fluid and electrolyte depletion, replacement may be necessary. Diarrhea was not observed in the nine human accidental exposure cases, but deposition of toxin on foodstuff could produce the syndrome. Diarrhea should be treated symptomatically.

Cough suppressants containing dextromethorphan or codeine should be employed initially for symptomatic therapy of respiratory symptoms. Prolonged coughing unrelieved by codeine might benefit from a semisynthetic, centrally acting narcotic antitussive containing hydrocodone (dihydrocodeinone). Monitoring of pulmonary status by pulse oximetry with prompt evacuation to a site with the capacity for intensive respiratory care by mechanical ventilation should be considered when respiratory status is compromised. No specific therapy has been identified or described for managing the respiratory effects of intoxication with aerosolized SEB. Experimental intervention in cytokine cascades has been a proposed therapy. Animal models have not yet indicated any therapeutic value for steroids.

PROPHYLAXIS

Immunotherapy

Infusion of intravenous gamma globulins has been successfully used[28,29] to treat episodes of Kawasaki disease (which is linked to the staphylococcal enterotoxins and TSST-1). Unpublished studies have documented prophylaxis and the therapeutic value of affinity-purified chicken anti-SEB antibody administered intravenously, in rhesus monkey inhalation of SEB. Monkeys given antibody just prior to, or 4 hours after, lethal challenge (5 LD_{50}, or 135 µg/kg) were protected from death. Although the animals survived, they did develop signs of intoxication. Efforts to devise both passive and active immunoprotection are being pursued. Because of the rapidity of MHC class II receptor binding by these toxins (apparent saturation < 5 min, in vitro), active immunity should be considered the best defense.[30]

Vaccines

A formalin-treated SEB toxoid has demonstrated some degree of efficacy in animal trials,[31] but has not yet been approved for human use. In an attempt to stimulate the requisite secretory antibody titers, a variety of different immunization routes and adjuvants have been explored, although the intramuscular immunization route has proven effective. Vaccines produced by genetic inactivation of the toxins have shown promising results in animal trials.[32] This strategy is based on substitution of active receptor-binding amino acid side chains to reduce affinities and consequential T-cell activation,[9] without altering the three-dimensional structure of the antigen. It is anticipated that this second-generation vaccine will be more antigenic and more likely to induce neutralizing antibodies than the toxoid.

SUMMARY

The staphylococcal enterotoxins are a family of superantigen protein toxins produced by strains of *Staphylococcus aureus*. Staphylococcal enterotoxin B (SEB), a toxin often associated with food poisoning, was weaponized as an incapacitating agent by the United States during in the 1960s. When inhaled as a respirable aerosol, SEB causes fever, severe respiratory distress, headache, and sometimes nausea and vomiting. The mechanism of intoxication is thought to be from a massive release of cytokines such as interferon-gamma, interleukin-6 and tumor necrosis factor–alpha. Diagnosis can be confirmed through the use of enzyme-linked immunosorbent assays of tissues or body fluids. Prophylactic administration of an investigational vaccine protects laboratory animals from inhalational challenge. Supportive care is useful in reducing toxicity in unprotected individuals.

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