Articles and Scientific Papers

St. Louis ME, Peck SHS, Bowering D, et al., 1988  
*Botulism from Chopped Garlic*  

*Botulism in the United States*  

Hughes JM, Blumenthal JR, Merson MH, et al., 1981  
*Clinical Features of Types A and B Food-borne Botulism*  

Villar RG, Shapiro RL, Busto S, et al., 1999  
*Outbreak of Type A Botulism and Development of a Botulism Surveillance and Antitoxin Release System in Argentina*  

MMWR, 1999  
*Outbreaks of Gastrointestinal Illness of Unknown Etiology Associated with Eating Burritos -- United States, October 1997-October 1998*  
Citation: MMWR. Outbreaks of Gastrointestinal Illness of Unknown Etiology Associated with Eating Burritos -- United States, October 1997-October 1998; MMWR 1999; 48(10):210-213.

FOR TRAINING USE ONLY: "BOTULISM IN ARGENTINA" COMPUTER-BASED CASE STUDY
Botulism from Chopped Garlic: Delayed Recognition of a Major Outbreak


Diagnosis of botulism in two teenaged sisters in Montreal led to the identification of 36 previously unrecognized cases of type B botulism in persons who had eaten at a restaurant in Vancouver, British Columbia, during the preceding 6 weeks. A case-control study implicated a new vehicle for botulism, commercial chopped garlic in soybean oil ($P < 10^{-4}$). Relatively mild and slowly progressive illness, dispersion of patients over at least eight provinces and states in three countries, and a previously unsuspected vehicle had contributed to prolonged misdiagnoses, including myasthenia gravis (six patients), psychiatric disorders (four), stroke (three), and others. Ethnic background influenced severity of illness: 60% of Chinese patients but only 4% of others needed mechanical ventilation ($P < 10^{-3}$). Trypsinization of serum was needed to show toxemia in one patient. Electromyography results with high-frequency repetitive stimulation corroborated the diagnosis of botulism up to 2 months after onset. Although botulism is a life-threatening disease, misdiagnosis may be common and large outbreaks can escape recognition completely.

**Botulism** is a neuropaalytic syndrome caused by the potent motor neurotoxin elaborated by *Clostridium botulinum*. Patients with botulism present with a characteristic pattern of neurologic symptoms and signs and typically have recently eaten home-canned foods (1). If the clinical presentation is unusual or if the patient had not recently eaten home-canned food, botulism may not be suspected. In September 1985, investigation of a multina-

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Methods

We defined a patient as a person who had been in or visited Vancouver between 15 July and 13 September 1985 and had symmetric cranial neuropathies and symmetric peripheral motor weakness that was otherwise unexplained. For a case-control study, the patient definition was further restricted to persons who had eaten at the restaurant between 29 August and 5 September and had symptoms or signs from both of the following categories: diplopia, ophthalmoplegia, or paresis; and dysphagia or dysarthria. Controls in the case-control study were
persons who ate at the restaurant with patients but developed no gastrointestinal or neurologic symptoms within the next 2 weeks; food histories and clinical laboratory findings of 22 patients and 22 controls were collected by investigators using questionnaires. Statistical tests of association used Fisher's two-tailed test.

Calculation of incubation periods excluded restaurant employees because the exact times of their food exposures were uncertain. Calculation of intervals to hospital admission excluded employees and patients who were hospitalized late for diagnostic procedures or for observation after their illness had stopped progressing. Attack rates were estimated for 1 to 5 September, when the restaurant had counted each menu item ordered.

Electromyography was done by consulting electrophysiologists using their own protocols. We considered low-frequency repetitive stimulation to be 2 to 5 Hz and rapid repetitive stimulation to be 20 to 50 Hz; findings of repetitive stimulation studies were included in this report if the interpretation of changes in the evoked train of compound muscle action potentials was based on a 10% or greater increase (incremental response) or decrease (decremental response) between the first and fifth evoked compound muscle action potential (2). Serum and stool were assayed for botulism toxin using the standard mouse inoculation assay with neutralization by type-specific antisera (1). Trypsinization of serum samples with 1% trypsin at 35°C for 45 minutes was done on some serum specimens before mouse inoculation. Stool was cultured for Clostridium botulinum by the chopped meat culture technique and with trypticase-peptone-glucose-yeast medium at 30°C.

We defined the working diagnosis as the diagnosis considered most likely by attending physicians when publicity or changes in the outbreak prompted diagnostic review, as determined by interview with physicians or chart reviews.

Results

Epidemiologic Findings

Botulism was identified in 4 restaurant employees and 32 patrons. Thirty patients lived in four provinces of Canada, 5 in three states in the United States, and 1 in the Netherlands. The ancestry of the patients was white European (24 patients), Chinese (10), Japanese (1), and Asian Indian (1). A case-control study of patients from the second cluster showed an association between illness and eating either a beef dip sandwich or a steak sandwich at the restaurant ($P < 10^{-8}$, Table 1). Between 1 to 5 September, 113 beef dip sandwiches were sold at the restaurant, and botulism was reported in 16 persons who ate the sandwich on those days, giving an estimated attack rate of 14%; some persons had eaten part but not all of the implicated sandwiches. In a comparison restricted to sandwich-eaters, the only common ingredient of the implicated sandwiches associated with illness was the garlic-buttered bread ($P < 10^{-4}$, Table 1); garlic butter was not used on any other items in the restaurant.

The garlic butter was made from bottled chopped garlic in soybean oil. The chopped garlic was rehydrated, sun-dried garlic without chemical or acid additives, and was labeled with instructions to refrigerate. Unopened bottles of garlic had reportedly been stored in the restaurant unrefrigerated for 8 months. One bottle of garlic, which some employees thought was spoiled, was apparently used during both outbreak periods but not between: it was used for days, then left unused on the rear of a refrigerator shelf, later recycled into use, and finally discarded for its offensive (to some) odor, thereby accounting for the biphasic epidemic curve and the termination of the outbreak before its detection (Figure 1). More than 2 months after the beginning of the outbreak and several days after the last patient ate at the restaurant, botulism was first diagnosed in patients, the restaurant identified, and implicated foods removed from the restaurant.

Clinical Findings

Symptoms were typical of botulism (Table 2), and were similar for the two clusters of cases. Twenty-four patients were hospitalized, 7 required mechanical ventilation, and none died. The median incubation period from ingestion of garlic to onset of neurologic symptoms was 2.3 days (range, 19 hours to 10 days, Figure 2), and the median interval from garlic ingestion to hospital admission for acute, progressive botulism was 7 days (range, 3

| Table 1. Consumption of Implicated Foods Causing Botulism by Patients and Controls, Vancouver, British Columbia, 29 August to 5 September 1985 |
|---|---|---|
| Food | Patients | Controls | $P$ Value\* |
| | n/a | n/a | |
| Beef dip sandwich | 20/22 | 3/22 | $10^{-6}$ |
| Beef dip or steak sandwich | 22/22 | 4/22 | $10^{-6}$ |
| Garlic-buttered bread† | 22/22 | 0/4 | $10^{-4}$ |

* Fisher two-tailed test.
† Comparison restricted to persons who ate the beef dip or steak sandwiches.
Table 2. Symptoms of Botulism

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Total with Data</th>
<th>Number with Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>$n (%)$</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Constipation</td>
<td>33</td>
<td>16 (48)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>33</td>
<td>33 (100)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>33</td>
<td>30 (91)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>33</td>
<td>29 (88)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>33</td>
<td>28 (85)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>33</td>
<td>27 (82)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>32</td>
<td>24 (73)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>33</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>31</td>
<td>6 (19)</td>
</tr>
</tbody>
</table>

to 13 days, Figure 2). One patient had a respiratory arrest 10 days after his meal at the restaurant; in 2 others, serial measurements of respiratory vital capacity declined steadily for more than 2 weeks after ingestion.

Electromyography was done in 24 patients, and electromyography with repetitive stimulation in 22. Rapid repetitive stimulation elicited an incremental response in the train of compound muscle action potentials in 11 of 12 botulism patients, but low-frequency stimulation produced a decremental response in only 3 of 16 patients. Rapid repetitive stimulation yielded a clear incremental response in 2 patients studied more than 2 months after onset of illness.

Sera from 3 of 21 patients collected a median of 10 days after onset of symptoms (range, 2 to 73 days) yielded type B botulism toxin. In 1 patient, toxin was detected on days 5 and 19 after ingestion in 0.5 mL of serum only after trypsinization. In a second patient, with mild symptoms who continued to work throughout his illness, the mouse assay detected toxin in 1.0 mL but not in 0.5 mL of trypsinized serum 14 days after eating at the restaurant. A third patient with toxaemia shown to have persisted at least 10 days during the first trimester of pregnancy later delivered a normal infant. No toxin was detected in stool specimens collected from 24 patients a median of 12.5 days after onset of symptoms, but one yielded proteolytic type B Clostridium botulinum. The epidemiologically implicated bottle of garlic had been discarded; other bottles still present in the restaurant did not yield botulinum toxin or Clostridium botulinum. Fifteen other bottles from the same production lot had a mean pH of 5.4 (range, 4.6 to 5.7). Proteolytic and nonproteolytic strains of type B Clostridium botulinum inoculated into bottles of the chopped garlic produced toxin within 2 weeks at 25°C.

Six of ten Chinese patients but only 1 of 26 other patients developed respiratory failure requiring mechanical ventilation (relative risk, 15.6; $P < 0.001$). As garlic butter was applied to sandwiches only in the restaurant kitchen and did not appear on the menu, those eating could not apply more or less garlic butter to their sandwiches. Each of the 30 patients with adequate food consumption histories reported eating most to all of one sandwich, except for 1 Chinese patron who ate less than half of a sandwich, 1 non-Chinese patron who ate 2.5 sandwiches, and 2 non-Chinese employees who ate two sandwiches each. The Chinese patients ate on 6 different days distributed over the duration of the outbreak; considering only patients who ate at the restaurant on those days, 6 of 10 Chinese patients but only 1 of 10 other patients required mechanical ventilation. In addition to ingested dose of toxin, the greater severity in Chinese patients could not be accounted for by different age or sex distribution of patients, presence of underlying diseases, or use of medications.

Information about the working diagnosis for patients with botulism when the outbreak was reported by the news media was available for 33 patients; botulism was correctly diagnosed or investigated a median of 13 days after onset of illness (range, 2 to 71 days). Myasthenia gravis, stroke, the atypical or descending variant of Guillain-Barré syndrome, psychiatric disorders, and viral syndromes were prominent among working diagnoses in botulism patients (Table 3), although most physicians remained concerned about atypical features in patients with these diagnoses. In 3 patients diagnosed as having strokes, neurologic deficits were symmetric, and no abnormalities were seen on cranial computerized tomographic scans. None of three patients with the working diagnosis of Guillain-Barré syndrome had an elevated cerebrospinal fluid protein level. On the other hand, tension challenge tests were clearly positive in 3 of 14 patients with botulism. Antibodies to acetylcholinesterase were reportedly detected in 1 of 8 patients with botulism tested, but the clinical and electrophysiologic data in this patient suggested botulism rather than myasthenia gravis. Psychiatric illness was diagnosed in 1 patient with ptosis, weakness, and swallowing deficits that led to nasal regurgitation and dehydration, and in a second patient who later suffered a respiratory arrest on a psychiatric ward.

Heightened awareness prompted more rapid diagnosis.

![Figure 2. Progression Illness in 19 Hospitalized Patients with Botulism Data exclude 5 hospitalized patients (2 restaurant employees and 3 patrons hospitalized after botulism had stopped progressing).](image-url)
Table 3. Working Diagnosis of 31 Patients with Botulism at the Time of Outbreak Recognition

<table>
<thead>
<tr>
<th>Working Diagnosis</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenia gravis</td>
<td>7</td>
</tr>
<tr>
<td>Psychiatric illness†</td>
<td>4</td>
</tr>
<tr>
<td>Viral syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Botulism‡</td>
<td>3</td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
</tr>
<tr>
<td>Guillaume-Barre syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Inflammatory myopathy</td>
<td>2</td>
</tr>
<tr>
<td>Diabetic complications</td>
<td>1</td>
</tr>
<tr>
<td>Hyperemesis gravidum</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
</tr>
<tr>
<td>Laryngeal trauma</td>
<td>1</td>
</tr>
<tr>
<td>Overexertion</td>
<td>1</td>
</tr>
</tbody>
</table>

* Excludes 5 patients first evaluated after the outbreak was recognized.
† Includes hysteria, agitated depression, separation reaction, factitious weakness.
‡ Includes the 3 family members whose diagnosis represented the initial recognition of the outbreak.

Neurologists from a single practice 500 miles from Vancouver followed one botulism patient through a 16-day hospitalization and a muscle biopsy with the working diagnosis of inflammatory myopathy. After a family member's reading about the Vancouver outbreak led to the proper diagnosis, members of the neurology practice identified botulism in an adolescent thought to have psychosomatic weakness, and in a person seeking a second opinion before having thymectomy for presumed myasthenia gravis; both were found to have eaten implicated sandwiches at the restaurant in Vancouver.

Discussion

Commercial chopped garlic in soybean oil, served on sandwiches in a restaurant in Vancouver, caused a prolonged outbreak of botulism between 27 July and 5 September 1985. One bottle of garlic used intermittently was apparently responsible for two discrete clusters of illness separated by almost a month. The implicated garlic was an aqueous mixture with a pH above 4.6 and had been stored at room temperature, conditions conducive to outgrowth of *C. botulinum* spores (3). Although commercial chopped garlic represents a new vehicle of botulinum intoxication, it resembles foods causing other recent botulism outbreaks: potato salad (4, 5) and sauteed onions (6). In each instance, the vehicle was a vegetable tuber or root that, after processing or cooking, was coated with oil, providing a relatively anaerobic environment for *C. botulinum* spores that had survived the low-temperature processing to germinate. The production of botulinum toxin in bottles of the commercial garlic at 25°C after experimental inoculation with *C. botulinum* spores showed that it must be refrigerated to prevent botulism. Acidification or other modification may thus be warranted in this and similar products to prevent botulism even if the product is mishandled.

Botulism in patients from the second cluster of cases in the Vancouver outbreak was confirmed by laboratory tests showing toxemia in several patients. While toxemia was not seen in patients from the early cluster, clinical, laboratory, and epidemiologic evidence corroborated that these patients had botulism. The dates of eating at the restaurant among the early cases were tightly clustered in time (Figure 1). Neurologic symptoms, the clinical course of illness, and the subsequent resolution of paralysis or paresis were all typical of botulism and were similar for patients from early and late clusters. Four of six patients from the early cluster had electromyographic findings characteristic of botulism; another contributed the only fecal specimen from either cluster that yielded type B *C. botulinum* (7). Finally, all nine patients in the early cluster with adequate food histories reported having eaten a sandwich with garlic butter at the implicated restaurant, the same food incriminated as the cause of the second cluster.

Long-delayed diagnosis of botulism has been reported frequently, including diagnosis only established retrospectively after death (8-11). In one review (12) of sporadic cases and small outbreaks, only 19 of 50 patients with botulism who required hospitalization were admitted during the initial physician contact. Diagnoses confused with botulism in the past include Guillain-Barré syndrome, myasthenia gravis, stroke, chemical intoxications, staphylococcal or other food poisoning, tick paralysis, diphtheria (1), cardiac failure (8, 11), bowel obstruction (8, 10), pharyngitis (8, 13), and others.

In this outbreak, symptoms of patients were typical of botulism (1, 12, 14); possibly atypical features were limited to the severity and temporal progression of illness, about which data are limited. The usual incubation period in botulism from ingestion of toxic food to onset of neurologic symptoms is thought to be 18 to 36 hours (14), and is similar in types A and B botulism (12). However, patients with type B disease consult physicians later after onset of illness and require mechanical ventilation less frequently (12), suggesting that type B botulism progresses more slowly and is less severe than type A. In addition, large outbreaks of botulism generally include patients with much milder illnesses than do small outbreaks or sporadic cases (15, 16), suggesting that subparalytic cases of botulism may frequently go unrecognized unless linked epidemiologically to other more severe cases. Similarly, milder cases of botulism are associated with longer incubation periods (6, 15), and the progression of the underlying pathophysiologic process (binding of toxin to and destruction of presynaptic neuromuscular end plates) (17) is clinically undetectable once patients with severe botulism are completely paralyzed. Therefore, it is possible that the apparent slow progression of illness in this outbreak is instead an artifact of the past underdiagnosis of mild, slowly progressive botulism.

This possibility is in accordance with the experience in Europe, where strains of *C. botulinum* are almost uniformly type B, and where milder forms of botulism than are traditionally seen in North America have been consistently reported (18). The infrequent detection of *C. botulinum* in the stools of the patients from this outbreak does not suggest in vivo toxin production by *C. botulinum* colonizing the intestine (19, 20).

Patients of Chinese descent suffered more severe illness from botulism than other patients, although we could
identify no basis for their having ingested more toxin. Reports from China do not indicate an overall severity of botulism that is unexpected by North American standards (21, 22). However, higher fatality rates have been reported for type B than for type A botulism in China (22), in sharp contrast to the consistently higher fatality rates for type A botulism in the United States (1). Although types A and B botulotoxin toxins have diverse effects on the neuromuscular junction in some animals (23), we can only speculate what pathophysiological mechanism, such as different affinities for receptor binding to toxin or different rates of serum proteolysis of circulating toxin molecules, might underlie these apparent ethnic differences in the severity of illness by toxin type.

The potentiation of toxicity by trypsinization is typical of the protoxin moiety from broth cultures of _C. botulinum_ (24) but has not been shown before in serum from human patients, in whom the protoxin molecule has been presumed to become fully activated by exposure to digestive enzymes during gastrointestinal absorption (8). The persistence of circulating protoxin (in an ethnic Chinese patient) may provide a clue to the slow progression of illness and to ethnic variation in the type-specific severity of botulism. In any case, this finding suggests that testing serum for toxin without previous trypsinization, as currently practiced (1), may sometimes give false-negative results.

Although repetitive stimulation electromyography studies in patients with botulism at high and low frequencies have been well described (2, 25), we found repetitive stimulation at high frequency much superior for eliciting findings of botulism. In addition, the decremental response to low-frequency stimulation seen with botulism is the same response seen in myasthenia gravis (2) and may be mistakenly interpreted in cases of botulism to support the diagnosis of myasthenia gravis, as occurred in several cases from this outbreak. Rapid repetitive stimulation should be used in cases of suspect myasthenia gravis with atypical features, as well as in cases of suspected strokes with symmetric neurologic deficits and normal neuroradiologic studies, in cases of suspected atypical (descending) Guillain-Barré syndrome without elevated cerebrospinal fluid protein levels, and in other settings where botulism might be a possibility. The advantages of electrophysiology studies up to 2 months after onset of illness make this a practical screening tool for possible botulism even when its application is delayed.

The remarkable, biphasic epidemic curve for this outbreak (Figure 1) reflects important features of the epide-miology of botulism. The second cluster of cases was recognized before the first, showing that at least 11 patients with botulism who had repeatedly consulted both internists and neurologists could escape diagnosis for longer than a month. The patients would not have been identified as having botulism without the publicity generated by the second cluster of cases. Timely recognition of the first outbreak could have prevented the substantial morbidity (5) and economic consequences (26) of the later cases of botulism due to the same vehicle. This outbreak suggests that botulism may be more common than is now thought and may frequently escape recognition, and shows why prompt diagnosis and investigation are so important. The rapid detection, investigation, and termination of a subsequent restaurant-associated outbreak in Vancouver in 1987 (27) suggest that heightened awareness in Vancouver led to recognition of botulism that might otherwise have gone undetected.

ACKNOWLEDGMENTS: The authors thank Nick Lusito, Bert Lukey, and Drs. Donald Huggins, Patricia Vogel, Matthew Leidlaw, Timothy Johnstone, Stanley Acres, Charles Hatheway, Andrew Penn, Howard Feldman, Gilbert Coll, Steven Kaysen, Steven Clark, and Rick Schreiber for their contributions; Barbara Fowler for statistical assistance; and Beverly Malone and Sara Waldrip for manuscript preparation.

Requests for reprints should be addressed to Michael St. Louis, M.D.; CIDDD:EDB-1 5428, Centers for Disease Control, Atlanta, GA 30333.

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References


Botulism is caused by a neurotoxin produced from the anaerobic, spore-forming bacterium *Clostridium botulinum*. Botulism in humans is usually caused by toxin types A, B, and E. Since 1973, a median of 24 cases of foodborne botulism, 3 cases of wound botulism, and 71 cases of infant botulism have been reported annually to the Centers for Disease Control and Prevention (CDC). New vehicles for transmission have emerged in recent decades, and wound botulism associated with black tar heroin has increased dramatically since 1994. Recently, the potential terrorist use of botulinum toxin has become an important concern.

Botulism is characterized by symmetric, descending, flaccid paralysis of motor and autonomic nerves, usually beginning with the cranial nerves. Blurred vision, dysphagia, and dysarthria are common initial complaints. The diagnosis of botulism is based on compatible clinical findings; history of exposure to suspect foods; and supportive ancillary testing to rule out other causes of neurologic dysfunction that mimic botulism, such as stroke, the Guillain-Barré syndrome, and myasthenia gravis. Laboratory confirmation of suspected cases is performed at the CDC and some state laboratories. Treatment includes supportive care and trivalent equine antitoxin, which reduces mortality if administered early. The CDC releases botulism antitoxin through an emergency distribution system. Although rare, botulism outbreaks are a public health emergency that require rapid recognition to prevent additional cases and to effectively treat patients. Because clinicians are the first to treat patients in any type of botulism outbreak, they must know how to recognize, diagnose, and treat this rare but potentially lethal disease.

Botulism is a neuroparalytic illness caused by a neurotoxin produced from the anaerobic, spore-forming bacterium *Clostridium botulinum* (1). Botulism was recognized as "sausage poisoning" during the 18th and 19th centuries (2), and the pathogenesis of disease was first described by van Ermengem in 1897 after his investigation of a large outbreak in Ellezelles, Belgium (3). Because botulinum toxin is so lethal, intensive surveillance and control measures have been mandated in the United States. However, prompt recognition and treatment of botulism by clinicians remain a critical component of surveillance and are the most important steps in reducing rates of death from this disease. Botulism outbreaks are a public health emergency that require rapid recognition to prevent additional cases and to effectively treat patients with mechanical ventilation and early administration of antitoxin. In the event of terrorist use of botulinum toxin, clinicians would also be the first to recognize and treat casualties of intentional botulism poisoning. In this report, we provide a clinical overview of botulism and describe the U.S. Botulism Surveillance System.

### The Organism

*Clostridium botulinum* is classified as a single species but consists of at least three genetically distinguishable groups of organisms. These are alike in their abilities to produce neurotoxins with similar pharmacologic activities (4) but diverse serologic properties (toxin types A, B, C, D, E, F, and G). Human botulism is primarily caused by the strains of *C. botulinum* that produce toxin types A, B, and E. Neurotoxigenic strains of *C. baratii* (5, 6) (which produce type F toxin) and *C. butyricum* (7) (which produce type E toxin) also have been implicated in human botulism. Strains of *C. botulinum* that produce type C or type D toxin for the most part cause botulism only in nonhuman species.

These neurotoxigenic organisms are anaerobic, gram-positive, spore-forming bacilli and are commonly found in soils throughout the world. *Clostridium botulinum* organisms cause food poisoning because the heat-resistant spores survive food preservation methods that kill nonsporulating organisms; they subsequently produce a potent neurotoxin under anaerobic, low-acid (pH > 4.6), and low solute conditions (8). The toxins affect a broad range of vertebrate species, but the evolutionary utility of toxin production to the bacterial host organisms is unclear.

### The Toxin

The seven recognized types of botulinum neurotoxins (types A through G) are distinguished by neutralization of biological activity with type-specific serologic reagents. These types are defined by the International Standards for *Clostridium botulinum* Antitoxin (9). The toxins of all types consist of a 100-kd heavy chain joined to a 50-kd light chain by a disulfide bond (10). After absorption into the bloodstream, botulinum toxin binds irreversibly to the presynaptic nerve endings of the peripheral nervous system and cranial nerves, where it inhibits the release of acetylcholine (Figure 1). The mechanism involves binding to a toxin receptor on the nerve cell membrane at the neuromuscular junction, internalization of a portion (the catalytic portion residing in the light chain) of the toxin molecule (11), and cleavage of protein components of the neuroexocytosis apparatus within the cell (12).

Botulinum neurotoxin is considered the most potent lethal substance known. It is 15 000 to 100 000 times more toxic than sarin, the potent organophosphate nerve agent used in a...
terrorist attack in the subway system in Tokyo (13). The nucleotide sequences for all seven toxin types have been sequenced (14-22).

Epidemiology

Four clinical forms of botulism occur in humans: foodborne botulism; wound botulism; infant botulism (infant intestinal colonization); and, rarely, adult infectious botulism (adult intestinal colonization). Studies in monkeys indicate that, if aerosolized, botulinum toxin also can be absorbed through the lungs (23); this could occur in the case of a terrorist attack. From 1973 through 1996 in the United States, 724 cases of foodborne botulism (median, 24 cases annually [range, 8 to 86 cases]), 103 cases of wound botulism (median, 3 cases annually [range, 0 to 25 cases]), 1444 cases of infant botulism (median, 71 cases annually [range, 0 to 99 cases]), and 39 cases of botulism of undetermined type were reported to the Centers for Disease Control and Prevention (CDC) (Figure 2) (CDC. Unpublished data). In the United States, approximately half of the cases of foodborne botulism are caused by toxin type A; the remaining foodborne cases are almost equally divided between toxins type E and type B (24). Among cases of infant botulism, approximately half are caused by toxin type A and half by toxin type B; among cases of wound botulism, approximately 80% are caused by toxin type A and 20% by toxin type B (CDC. Unpublished data). In the United States, type A botulism is most common west of the Mississippi River, and type B is most common east of the Mississippi River (25). Type E outbreaks are most common in Alaska (26, 27).

Important changes in the epidemiology of botulism have emerged in the past few decades. Recently identified vehicles for foodborne botulism include homemade salsa (24), baked potatoes sealed in aluminum foil (28), cheese sauce (29), sautéed onions held under a layer of butter (30), garlic in oil (31), and traditionally prepared salted or fermented fish (26) (Table 1). From 1976 through 1984, restaurant-associated outbreaks accounted for a large proportion of botulism cases (42%), although only 4% of all outbreaks were restaurant-associated (32). The largest of these outbreaks were caused by jalapeño peppers in Michigan in 1977, potato salad in New Mexico in 1978, sautéed onions in Illinois in 1983, and skordalia made with baked potatoes in Texas in 1994 (33).

In 1995 and 1996, the occurrence of wound botulism increased (34), with a total of 42 cases (CDC. Unpublished data). Most of these cases occurred among heroin users in California who injected the drug subcutaneously. Although it is unclear what factors contributed to this epidemic, a shift to the use of black tar heroin produced in Mexico may have played a role (35).

Purified botulinum toxin is used to treat various medical conditions, such as strabismus, blepharospasm, torticollis, oromandibular dystonia, spasmodic dysphonia, and achalasia. Systemic symptoms of botulism-like illness have been reported after therapeutic administration of botulinum toxin (36) but are unlikely to have resulted from this procedure. It is estimated that for most patients, at least 10 times the treatment dose would be required to enter the circulation for systemic symptoms to result (37; CDC. Unpublished data).

The potential for intentional poisoning with botulinum toxin has come into clearer focus in recent years. As many as 17 countries are suspected to include or to be developing biological agents in their offensive weapons programs (38). Botulinum toxin often is one of these agents because it is relatively easy to produce and is highly lethal in small quantities. In August 1995, Iraq revealed that during the Persian Gulf War, 11 200 L of botulinum
toxin preparation was loaded into specially designed SCUD missile warheads (39). In addition, before the Aum Shinrikyo used sarin in the 1995 terrorist attack on the Tokyo subway system, the cult had produced botulinum toxin (40).

**Clinical Features**

**Foodborne Botulism**

Foodborne botulism is caused by ingestion of preformed toxin produced in food by *C. botulinum*. The most frequent source is home-canned foods, in which spores that survive an inadequate cooking and canning process germinate, reproduce, and produce toxin in the anaerobic environment of the canned food. In the event of intentional foodborne poisoning with botulinum toxin, the signs and symptoms developing after ingestion would probably resemble those of naturally occurring foodborne botulism. If aerosolized toxin was inhaled, the incubation period might be slightly longer (23), and gastrointestinal symptoms might not occur.

The clinical syndrome of foodborne botulism is dominated by neurologic symptoms and signs resulting from a toxin-induced blockade of the voluntary motor and autonomic cholinergic junctions (Table 2). Although the syndrome is similar for each toxin type, type A toxin has been associated with more severe disease and a higher fatality rate than type B or type E toxin (41). Symptoms from any toxin type may range from subtle motor weakness or cranial nerve palsies to rapid respiratory arrest. The initial symptoms of foodborne botulism may be gastrointestinal and can include nausea, vomiting, abdominal cramps, or diarrhea; after the onset of neurologic symptoms, constipation is more typical. Dry mouth, blurred vision, and diplopia are usually the earliest neurologic symptoms. These initial symptoms may be followed by dysphonia, dysarthria, dysphagia, and peripheral muscle weakness. Symmetric descending paralysis is characteristic of botulism; paralysis begins with the cranial nerves, then affects the upper extremities, the respiratory muscles, and, finally, the lower extremities in a proximal-to-distal pattern. Onset usually occurs 18 to 36 hours after exposure (range, 6 hours to 8 days) (42). In severe cases, extensive respiratory muscle paralysis leads to ventilatory failure and death unless supportive care is provided. Patients have required ventilatory support for up to 7 months before the return of muscular function, but ventilatory support is most commonly needed for 2 to 8 weeks (43).

Clinical recovery generally occurs over weeks to months; electron microscopic evidence suggests that clinical recovery correlates with the formation of new presynaptic end plates and neuromuscular junctions (44, 45). Before mechanical ventilation and intensive supportive care, up to 60% of patients died; since the 1950s, however, the mortality rate from botulism has steadily decreased (43). Death now occurs in 5% to 10% of cases of foodborne botulism; early deaths result from a failure to recognize the severity of disease, whereas deaths after 2 weeks result from complications of long-term mechanical ventilatory management (42).

**Wound Botulism**

Wound botulism occurs when anaerobic conditions within an abscessed wound allow germination of *C. botulinum* spores, subsequent multiplication of the organism, and production and absorption of toxin in vivo. The clinical manifestations are similar to those seen in foodborne botulism, except that gastrointestinal symptoms are absent and the
median incubation period is longer (7 days [range, 4 to 14 days]) (46). The case-fatality rate for wound botulism is approximately 15% (47).

**Infant Botulism**

Botulism in infants due to intestinal colonization represents a distinct clinical entity in which *C. botulinum* spores enter and colonize the gastrointestinal tract and produce toxin. The disease most commonly occurs during the second month of life. Constipation is usually the earliest clinical sign, followed by poor feeding; lethargy; a weak cry; decreased sucking; and generalized lack of muscle tone, noticeably characterized by a floppy head (48). The spectrum of disease is wide, ranging from mild constipation to sudden death, although recovery generally occurs over weeks to months (49). The source of ingestion is unknown in approximately 85% of cases; in up to 15% of cases, the ingestion of honey is suspected (49, 50). The risk factors for infant botulism are poorly described; for unclear reasons, the disease does not occur in outbreaks, and it is thought that host susceptibility factors may play an important role (50).

**Adult Infectious Botulism**

In rare instances, botulism in adults also can occur as a result of intestinal colonization with *C. botulinum* and in vivo toxin production in a manner similar to that of infant botulism (51, 52). Such patients often have a history of abdominal surgery, gastrointestinal tract abnormalities, or recent antibiotic treatment that may disrupt the natural gastrointestinal flora (53, 54). Cases have been caused by toxin types A and B; in addition, three cases involving type F toxin produced by *C. barati* were confirmed by the CDC (6, 24).

**Diagnosis**

**Clinical Findings**

Botulism is underdiagnosed because many clinicians are unfamiliar with the disease and because symptoms can be mistaken for more common clinical entities, such as stroke or the Guillain-Barré syndrome (52, 55). However, the diagnosis of botulism is not difficult in most cases once it has been considered. Botulism should be suspected in a patient with acute onset of gastrointestinal, autonomic (such as dry mouth or difficulty focusing eyes), and cranial-nerve (diplopia, dysarthria, dysphagia) dysfunction. The diagnosis is even more likely if the patient has recently eaten home-canned foods or if family members or companions who have shared meals are similarly ill.

**Ancillary Testing**

Because of the importance of early treatment, botulism must be diagnosed initially on the basis of the history and physical findings before toxin testing and culturing can be performed. The differential diagnosis for botulism includes the Guillain-Barré syndrome (especially the Miller-Fisher variant), myasthenia gravis, the Eaton-Lambert syndrome, and the stroke syndrome; intoxication with organophosphates, atropine, carbon monoxide, or aminoglycosides; and tick paralysis, paralytic shellfish poisoning, and puffer fish ingestion (55). The diagnosis of botulism is supported by ancillary testing (Table 3), such as documentation of a normal result on magnetic resonance imaging or computed tomography of the brain to rule out stroke syndrome; a normal result on lumbar puncture to differentiate
botulism from the Guillain-Barré syndrome, which typically causes elevated levels of protein in the cerebrospinal fluid (although protein levels may be normal initially); and a negative edrophonium chloride test result to rule out myasthenia gravis (although transient responses may occasionally be noted in botulism). Electromyography usually reveals decreased amplitude of action potentials in affected muscle groups, but this finding is relatively nonspecific. An incremental increase in amplitude to rapid repetitive electromyography by using frequencies of 20 to 50 Hz is more helpful and may distinguish botulism from the Guillain-Barré syndrome or myasthenia gravis but not the Eaton-Lambert syndrome. Electromyography should be performed by a person experienced in performing rapid repetitive testing (55).

In most cases, lumbar puncture and brain imaging can be performed within hours of presentation. Negative results may raise the clinical suspicion for botulism and should prompt close monitoring for respiratory compromise; rapid repetitive electromyography; and, possibly, edrophonium chloride testing. State or local health officials should be contacted to discuss potential measures for preventing additional cases; the possible release of antitoxin by CDC; and the collection of serum and stool samples at the earliest possible opportunity to confirm the diagnosis of botulism by the detection of toxin if none of the ancillary tests is pathognomonic.

**Toxin and Microbiological Testing**

In cases of suspected foodborne botulism, serum and stool specimens and epidemiologically implicated foods should be tested for botulism neurotoxin. The most reliable method for the detection of toxin is the mouse inoculation test; this can be performed at the CDC or some state public health laboratories. Botulinum toxin type is determined by neutralizing the biological activity of toxic samples injected into mice with type-specific botulism antitoxin. Symptoms of botulism and death occur in mice injected with unneutralized samples but not in mice injected with neutralized samples (56). Efforts to replace mouse inoculation testing with in vitro tests for botulism antitoxin, such as enzyme-linked immunosorbent assays (57) or polymerase chain reaction (58), remain experimental.

Toxin is detected in serum or stool specimens in approximately 46% of clinically diagnosed cases. Stool specimens also should be cultured for *C. botulinum* because a positive *C. botulinum* culture from stool is also considered confirmatory for botulism. Isolation of neurotoxigenic organisms from stool specimens increased the sensitivity of laboratory testing to 73% in one case series (59) and 67% in another (41). Detection of botulinum toxin from epidemiologically implicated food may provide additional confirmatory evidence for botulism; however, the isolation of *C. botulinum* organisms from a food devoid of toxin usually has little significance because spores are ubiquitous in the environment. If wound botulism is suspected, such specimens as wound exudate, a tissue sample, or a swab sample should be obtained for anaerobic culture in addition to a serum toxin assay. A stool specimen may be examined to exclude food or intestinal colonization as sources of toxin. Infant botulism should be suspected in any infant with constipation, poor feeding, diminished sucking and crying ability, neck and peripheral muscle weakness, or ventilatory distress. Stool cultures for *C. botulinum* and testing for the presence of toxin in stool should be performed in such patients.

**Management**
Individual Patients

Supportive Measures

The mainstay of treatment for severe botulism is supportive therapy with mechanical ventilation, which has substantially decreased mortality rates in the past 40 years. Because respiratory arrest may be rapid, patients suspected of having botulism should be monitored initially in an intensive care unit, the vital capacity should be checked frequently, and mechanical ventilation should be initiated at the earliest signs of respiratory decompensation. In addition, gastric lavage should be attempted if the potential food exposure was recent; in the absence of profound ileus, cathartic agents or enemas may be useful for removing unabsorbed toxin from the gastrointestinal tract. Cathartic agents containing magnesium should be avoided because of the theoretical concern that increased magnesium levels may enhance the action of botulinum toxin. If wound botulism is suspected, surgical debridement should be performed and antimicrobial treatment (such as penicillin) should be given.

Antitoxin Administration

The administration of antitoxin is the only specific pharmacologic treatment available for botulism. The currently available licensed antitoxin is an equine product with antibodies to toxin types A, B, and E. The administration of trivalent equine antitoxin to humans by the intravenous route neutralizes toxin molecules that are not yet bound to nerve endings. Before 1996, two to four 10-mL vials were administered to each adult patient suspected of having botulism; however, one vial (7500 IU of type A, 5500 IU of type B, and 8500 IU of type E antitoxins) per patient is now administered, and it is believed that no additional doses are necessary. Each vial contains an amount of antitoxin that is more than 100-fold greater than that needed to neutralize the largest amount of circulating antitoxin ever measured at the CDC (60). The circulating antitoxins have a half-life of 5 to 8 days, and a hypersensitivity reaction has been reported for up to 9% of patients (60, 61). After the change to single-vial dosing, the incidence of hypersensitivity may be smaller than that previously reported.

If it is administered early during the course of neurologic dysfunction, antitoxin is effective in preventing progression of illness and shortening the duration of ventilatory failure in severe cases of botulism (62). A retrospective analysis of 134 cases of type A botulism showed an overall mortality rate of 10% among patients who received early treatment with antitoxin (within 24 hours of symptom onset) compared with 15% among those who received late treatment (more than 24 hours after symptom onset) and 46% among those who did not receive antitoxin. In addition, survivors who received antitoxin early had a median hospital stay of only 10 days compared with 41 days for those who received antitoxin late and 56 days for those who did not receive antitoxin (62). More than 80% of patients with adult infectious botulism in the United States are treated with antitoxin. The remaining 20% generally have such a prolonged delay in diagnosis that treatment is considered to be of no benefit; therefore, antitoxin is not administered. Equine antitoxin therapy has not been recommended for infant botulism because of early observations (since disproved) that serum toxin was not detected in such cases and because of concerns about hypersensitivity reactions to this product (61). The safety and efficacy of a human-derived antitoxin product (human botulism immune globulin) administered to infants with botulism are being determined (49). As of June 1998, this product is available in the United States.
solely for the treatment of infant botulism, under a Treatment Investigational New Drug protocol. For information on obtaining human botulism immune globulin, contact the California Department of Health Services at 510-540-2646 (24 hours).

Management of Large Outbreaks

In the event of a large outbreak of botulism caused by an enteric or aerosolized route of exposure, the primary means of treating victims would be supportive care through the rapid mobilization of mechanical ventilators. Emergency support with intubation and manual ventilation would be critical during the early hours. Rapid administration of botulism antitoxin is the only pharmacologic treatment available and would probably reduce mortality rates. In U.S. Army experiments, equine F(ab')2 botulism antitoxin given therapeutically to rhesus monkeys as late as 24 hours after an aerosol challenge with a lethal dose of type A toxin resulted in high rates of survival. Without mechanical ventilation, however, the toxin was uniformly lethal if antitoxin administration was delayed until clinical signs had occurred (29 to 46 hours after exposure) (12). Prophylactic immunization with a vaccine against botulinum toxin would also protect against an exposure to botulinum toxin. However, the botulism toxoid vaccine is unlicensed, and the vaccination process must be started months before exposure. The vaccine does not provide life-long immunity, and administration is impractical except for a select high-risk group (such as laboratory workers who work with botulism specimens or military personnel with risk for exposure in battlefield conditions). In most instances, if exposure to a food contaminated by botulinum toxin is suspected in an outbreak setting, asymptomatic persons should be monitored closely without specific therapy and treatment with antitoxin should be initiated at the earliest signs of illness.

Surveillance and Public Health Response

Because cases of foodborne botulism result from ingestion of contaminated food that may still be available to cause illness in others, a single case of foodborne botulism represents a public health emergency and may herald the beginning of a larger outbreak. Investigation of a suspected case of botulism includes a search for other possible cases, identification of suspect food exposures, and diagnostic testing of both cases and foods as needed. Rapid assessment to determine the source of contamination can lead to appropriate control measures, such as impounding home-canned foods, closing a restaurant, or instituting an emergency product recall. Efforts to locate persons exposed to the same suspect food may lead to early diagnosis in persons in whom the diagnosis might otherwise be missed altogether.

The CDC maintains intensive surveillance for cases of botulism in the United States in collaboration with state health departments. To identify possible outbreaks rapidly, the CDC provides epidemiologic consultation and laboratory diagnostic services to state and local health departments for suspected cases of foodborne and wound botulism and supplies antitoxin for probable cases at the request of state health departments. Physicians are encouraged to contact their state epidemiologists as soon as they suspect botulism in a patient. State epidemiology offices maintain emergency contact numbers and can assist in diagnosing, managing, and preventing botulism. Epidemiologists from the Foodborne and Diarrheal Diseases Branch at the CDC are available 24 hours a day to answer calls from state health officials treating potential cases of botulism (telephone 404-639-2206; emergency telephone 404-639-2888). In collaboration with state epidemiology offices, CDC
epidemiologists recommend appropriate laboratory testing (performed at the CDC or in state laboratories) and ancillary studies to confirm or rule out the diagnosis. Local public health authorities and national food safety authorities should be involved as soon as foodborne botulism is suspected so that possible sources can be investigated and the need for further investigation and preventive measures can be determined.

When foodborne, wound, or adult infectious botulism is suspected, antitoxin is released from CDC quarantine stations. The rapid investigation of cases by local health officials, state epidemiologists, and the CDC prevents additional cases of botulism from implicated foods. Because infant botulism does not occur in outbreaks, the rapid consultation and response mechanism is not used for cases of infant botulism. If human botulism immune globulin, the human antitoxin product under investigation for treatment of infants, is licensed for distribution (49), it will be made available in a separate formulation for use in infants only. Until licensure, the California Department of Health Services can be contacted for information on human botulism immune globulin.

Conclusions

Botulism is a rare but potentially fatal illness, and prompt recognition of the clinical syndrome plays an important role in decreasing mortality rates. Physicians trained in internal medicine, emergency medicine, critical care, neurology, and infectious diseases may be needed to coordinate case-management efforts as soon as the diagnosis is suspected and before laboratory confirmation of the toxin. In a foodborne outbreak or an intentional poisoning, clinicians may be the first to recognize an ongoing public health emergency. State and local epidemiologists should be informed of all suspected botulism cases to determine potential vehicles of transmission, prevent additional cases, and obtain samples of implicated foods for testing. Epidemiologists at the CDC are available 24 hours a day for clinical consultation and release of antitoxin when appropriate.

In memoriam: Dr. Charles Hatheway passed away after this manuscript was completed. Dr. Hatheway dedicated his life to the study of botulism and contributed significantly to our understanding of this disease. He will be greatly missed.

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Clinical Features of Types A and B Food-borne Botulism

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Medical records of 55 patients with type A and type B food-borne botulism reported to the Centers for Disease Control during 2 years were reviewed to assess the clinical features and severity of illness, diagnostic test results, nature of complications, and causes of death. Some patients had features not usually associated with botulism including paresthesia (14%), asymmetric extremity weakness (17%), asymmetric ptosis (8%), slightly elevated cerebrospinal fluid protein values (14%), and positive responses to edrophonium chloride (26%). Several observations suggest that type A was more severe than type B disease. Although the case-fatality ratio was not significantly greater, patients with type A disease saw a physician earlier in the course of illness, were more likely to need ventilatory support, and were hospitalized longer. Patients who died were older than those who survived. Deaths within the first 2 weeks resulted from failure to recognize the severity of the disease or from pulmonary or systemic infection whereas the three late deaths were related to respirator malfunction.

BOTULISM caused by food contaminated with a neurotoxin of Clostridium botulinum is an uncommon disease in the United States. Types A and B botulinic toxin accounted for 87% of outbreaks and 91% of cases of known toxin type reported to the Centers for Disease Control (CDC) from 1970 through 1979 (1-3).

Because the disease is rare, most clinicians have never seen a case. Textbook descriptions have frequently been based on clinical data from individual botulism outbreaks (4-10) and may not provide a perspective on the range of clinical features, severity, duration, and complications of disease caused by different toxin types.

In this paper we describe the results of a systematic review of clinical records on 55 cases of types A and B food-borne botulism reported to CDC. Such an analysis allows comparison of clinical features and severity of illness, diagnostic test results, nature of complications, and causes of death and provides an assessment of the frequency of atypical clinical features.

Methods

Hospital or physician office records for each patient with botulism reported to CDC in 1973 to 1974 were reviewed, and clinical and laboratory data were recorded on a standardized form. Most records were reviewed by two of the authors; several were reviewed by other CDC physicians after instructions from the authors. Symptoms and signs were considered present if specifically noted in the record and not present only if specifically stated to be absent.

An outbreak was considered laboratory confirmed if toxin was found in the serum or stool of at least one ill patient or in the epidemiologically incriminated food by the mouse toxin neutralization test or if C. botulinum was isolated from feces of an ill person or from implicated food (I, II, 12). Data were analyzed with Fisher’s two-tailed exact test and the Mann-Whitney U test.

Results

During the 2 years, 35 botulism outbreaks involving 68 patients were reported; toxin types A and B accounted
for 29 of the outbreaks and 56 (82%) of the patients. Review of clinical records was completed for 55 (98%) of the 56 patients. The age and sex distributions of the 26 patients with type A botulism (mean age 50 years, 17 female) were similar to those of the 29 patients with type B disease (mean age 42 years, 18 female).

**CLINICAL FEATURES**

Mean incubation periods for patients with type A and type B botulism were similar. Twenty-five patients with type A and 25 with type B botulism were hospitalized. The commonest symptoms were dysphagia, dry mouth, diplopia, and dysarthria (Table 1). Of note is that five patients with type A and three with type B botulism complained of paresthesia. Acute gastrointestinal symptoms (nausea, vomiting, abdominal cramps, or diarrhea) were present within 2 hours after onset of illness in 15 patients with type A and in 14 with type B botulism. Dysarthria, blurred vision, dyspnea, diarrhea, sore throat, and dizziness occurred significantly more frequently in patients with type A botulism.

Pupillary findings were recorded for most patients during the initial physical examination. Dilated pupils were present initially in only four of 23 patients with type A compared with 12 of 26 with type B botulism ($p = 0.04$); none of 24 patients with type A and nine of 27 patients with type B botulism had nonreactive pupils on initial evaluation ($p = 0.002$).

Weakness of the upper and lower extremities, paresis, and hypoactive gag reflex were present in over 50% of patients with either type A or B botulism (Table 2). Extremity weakness was asymmetric in one of 16 patients with type A and four of 14 patients with type B botulism, whereas paresis was asymmetric in two of 22 patients with type A and one of 16 with type B botulism. Arm weakness, paresis, extracranial muscle weakness, facial nerve dysfunction, tone weakness, and nystagmus occurred significantly more frequently in patients with type A botulism. Patients with type A disease were less likely to have normal deep tendon reflexes.

Whereas 24 patients with type A botulism saw a physician within 3 days of onset of illness, only nine patients with type B disease did so. Patients with type A botulism saw physicians significantly earlier than those with type B disease ($p < 0.001$). However, only nine of 25 patients with type A and 10 of 25 patients with type B botulism who required hospitalization were admitted during the initial physician contact.

### Table 1. Symptoms of Types A and B Food-borne Botulism

<table>
<thead>
<tr>
<th>Physical Finding</th>
<th>Type A*</th>
<th>Type B*</th>
<th>$p$</th>
<th>Type A or B†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>24/25</td>
<td>28/29</td>
<td>NS</td>
<td>96</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>15/18</td>
<td>25/25</td>
<td>NS</td>
<td>93</td>
</tr>
<tr>
<td>Diplopia</td>
<td>18/20</td>
<td>24/26</td>
<td>NS</td>
<td>91</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>16/26</td>
<td>20/29</td>
<td>0.002</td>
<td>84</td>
</tr>
<tr>
<td>Upper extremity weakness</td>
<td>18/21</td>
<td>18/28</td>
<td>NS</td>
<td>73</td>
</tr>
<tr>
<td>Lower extremity weakness</td>
<td>16/21</td>
<td>18/28</td>
<td>NS</td>
<td>69</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>16/24</td>
<td>10/24 &lt; 0.001</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21/23</td>
<td>10/29 &lt; 0.001</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Paresis</td>
<td>2/10</td>
<td>3/25</td>
<td>NS</td>
<td>14</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>8/11</td>
<td>19/26</td>
<td>NS</td>
<td>73</td>
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<tr>
<td>Nausea</td>
<td>16/22</td>
<td>16/28</td>
<td>NS</td>
<td>64</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16/23</td>
<td>14/28</td>
<td>NS</td>
<td>59</td>
</tr>
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<td>Abdominal cramps</td>
<td>4/12</td>
<td>11/24</td>
<td>NS</td>
<td>42</td>
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<tr>
<td>Diarrhea</td>
<td>6/17</td>
<td>2/26</td>
<td>NS</td>
<td>19</td>
</tr>
<tr>
<td>Miscellaneous symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>12/13</td>
<td>18/26</td>
<td>NS</td>
<td>77</td>
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<tr>
<td>Sore throat</td>
<td>12/16</td>
<td>9/23</td>
<td>0.05</td>
<td>54</td>
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<tr>
<td>Dizziness</td>
<td>12/14</td>
<td>7/23</td>
<td>0.002</td>
<td>51</td>
</tr>
</tbody>
</table>

* Number of patients with finding per number in whom data were available.
† NS= not significant.
†† Percent of patients with symptoms.

### Table 2. Physical Findings in Patients with Types A and B Food-borne Botulism

<table>
<thead>
<tr>
<th>Physical Finding</th>
<th>Type A*</th>
<th>Type B*</th>
<th>$p$</th>
<th>Type A or B†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper extremity weakness</td>
<td>21/23</td>
<td>18/29</td>
<td>0.02</td>
<td>75</td>
</tr>
<tr>
<td>Paresis</td>
<td>22/23</td>
<td>16/29</td>
<td>0.001</td>
<td>73</td>
</tr>
<tr>
<td>Lower extremity weakness</td>
<td>18/22</td>
<td>17/29</td>
<td>NS</td>
<td>69</td>
</tr>
<tr>
<td>Hypoactive gag reflex</td>
<td>17/21</td>
<td>15/28</td>
<td>NS</td>
<td>65</td>
</tr>
<tr>
<td>Extracranial muscle</td>
<td>20/23</td>
<td>13/28</td>
<td>0.003</td>
<td>65</td>
</tr>
<tr>
<td>Facial nerve dysfunction</td>
<td>16/19</td>
<td>13/27</td>
<td>0.02</td>
<td>63</td>
</tr>
<tr>
<td>Tongue weakness</td>
<td>20/22</td>
<td>8/26 &lt; 0.001</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Pupils fixed or dilated</td>
<td>6/18</td>
<td>10/18</td>
<td>NS</td>
<td>44</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>8/18</td>
<td>1/23</td>
<td>0.003</td>
<td>22</td>
</tr>
<tr>
<td>Ataxia</td>
<td>4/17</td>
<td>3/24</td>
<td>NS</td>
<td>17</td>
</tr>
<tr>
<td>Initial mental status</td>
<td>22/25</td>
<td>25/27</td>
<td>NS</td>
<td>90</td>
</tr>
<tr>
<td>Alert</td>
<td>1/23</td>
<td>1/27</td>
<td>NS</td>
<td>4</td>
</tr>
<tr>
<td>Lethargic</td>
<td>2/25</td>
<td>1/27</td>
<td>NS</td>
<td>6</td>
</tr>
<tr>
<td>Obtunded</td>
<td>2/25</td>
<td>1/27</td>
<td>NS</td>
<td>6</td>
</tr>
<tr>
<td>Deep tendon reflexes</td>
<td>8/24</td>
<td>20/28</td>
<td>0.01</td>
<td>54</td>
</tr>
<tr>
<td>Normal</td>
<td>8/24</td>
<td>20/28</td>
<td>0.01</td>
<td>54</td>
</tr>
<tr>
<td>Hypoactive or absent</td>
<td>13/24</td>
<td>8/28</td>
<td>NS</td>
<td>40</td>
</tr>
<tr>
<td>Hyperactive</td>
<td>3/24</td>
<td>0/28</td>
<td>NS</td>
<td>6</td>
</tr>
</tbody>
</table>

* Number of patients with finding per number in whom data were available.
† NS= not significant.
‡ Percent of patients with symptoms.

**DIAGNOSTIC TESTS**

Three of 14 patients with type A botulism had a cerebrospinal fluid protein concentration between 50 and 60 mg/dL; protein values were normal in patients with type B botulism. Edrophonium chloride tests were done in 19 patients with type A and eight patients with type B disease; five with type A and two with type B disease had a positive response. However, the response was not dramatic.

Electromyograms were done for 10 patients with type A and nine with type B disease; II of 13 with data available had decreased amplitude of the muscle-action potential. Eight of 13 had evidence of facilitation of the muscle-action potential after tetanic stimulation or during rapid repetitive stimulation at rates of 20/s or more; patients with type B botulism showed facilitation more frequently ($p = 0.005$).
THERAPY

Twenty-two of the 26 patients with type A and 21 of the 29 patients with type B disease received botulinum antitoxin. Ten of the 12 patients who did not receive antitoxin either had mild illness or died before diagnosis; the other two patients had begun to recover before the diagnosis was made.

OUTCOME

Cardiorespiratory arrest occurred before initiation of ventilatory assistance in nine of 26 patients with type A and four of 29 with type B botulism. Nine of 13 patients who had respiratory arrest before intubation died compared with one of 15 of those intubated electively \( (p = 0.001) \). No arrest occurred before a patient saw a physician, and only one occurred before hospitalization.

Patients with type A botulism needed ventilatory support more frequently than those with type B botulism \( (21 \text{ of } 26 \text{ versus } 7 \text{ of } 29, p < 0.001) \). Although patients with type A botulism needed more prolonged ventilatory support \( \text{(mean of } 58 \text{ versus } 26 \text{ days}) \), the difference was not significant. Patients with type A botulism were hospitalized for a mean of 63 days compared with a mean of 21 days from those with type B disease \( (p < 0.03) \).

Seven patients with type A and three patients with type B botulism died. Patients who died were older \( \text{(mean age, } 57 \text{ years)} \) than those who survived \( \text{(mean age, } 43 \text{ years)} \) \( (p = 0.06) \). There was no difference in time from onset of illness to diagnosis or time from onset of illness to antitoxin therapy for fatal and nonfatal cases. Deaths within 2 weeks after onset were related to failure to recognize the gravity of the disease, or to pulmonary or systemic infection, or to both. The three deaths that occurred after 2 weeks were related to malfunction of respirators.

Discussion

Because CDC distributes botulinum antitoxin, most cases in which the diagnosis of botulism was considered were probably reported. However, some mild cases probably occurred that did not result in a visit to a physician, and diagnoses may not have been made in some severe and even fatal cases. Although the data suffer from limitations inherent in retrospective analyses of clinical records, most patients did have detailed histories and frequent recording of physical findings. Moreover, many attending physicians spoke with the authors early in the course of illness, resulting in some uniformity of clinical data.

Botulism is typically characterized by symmetric descending weakness or paralysis in the absence of sensory abnormalities. Patients are alert and afebrile early in the illness \( (1) \). Our observations, however, indicate that some patients may have atypical features and that the diagnosis should not be excluded because of one or two unexpected findings. For example, 14\% of patients reported paresthesia; this sensory symptom is one that is often used to differentiate patients with Guillain-Barré syndrome from those with botulism. A similar frequency of paraesthesia was noted in a recently reported type B botulism outbreak \( (9) \). Nystagmus and ataxia were observed in 22\% and 17\% of patients, respectively. Asymmetry of neurologic findings, occasionally reported by others \( (13) \), was noted in 19\% of patients. Pupillary abnormalities are frequently associated with botulism; however, our data and observations of Cherigton \( (14) \), who reported normal pupils in 12 of 14 patients, indicate that pupils are often normal, especially early in the illness.

Three tests used to evaluate patients with suspected botulism are lumbar puncture, the edrophonium chloride test, and electromyography. Evaluation of cerebrospinal fluid may be useful in distinguishing patients with botulism from those with Guillain-Barré syndrome, although patients with Guillain-Barré syndrome may have normal spinal fluid during the first 1 or 2 weeks of illness \( (15) \). Three patients in this study had slightly elevated protein levels. A similar abnormality has been reported in a patient with type E botulism whose spinal fluid protein level was 68 mg/dL \( (4) \). Data from this study and from Cherigton's series \( (14) \) suggest that positive edrophonium chloride test results should not be used to eliminate the diagnosis. Electromyographic studies in patients with botulism frequently show characteristic abnormalities in clinically involved muscle groups \( (16, 17) \). However, 15\% of patients had normal muscle action potential amplitudes, and 38\% lacked evidence of facilitation.

Previously reported case-fatality ratios have suggested that type A may be more severe than type B botulism \( (1) \). Both similarities and a number of important differences were noted in disease caused by the two toxin types. The age distributions, incubation periods, and frequency of hospitalization were similar. Although the case-fatality ratio was higher and patients with type A disease needed more prolonged ventilatory support, these differences were not significant. However, several observations do support the hypothesis that type A disease is more severe. Patients with type A disease saw physicians earlier in their illness, were more likely to require ventilatory support, and were hospitalized longer than those with type B disease.

The explanation for the apparent increased severity of type A compared with type B botulism is speculative. The two toxins have similar toxicity by the intraperitoneal route \( (18) \). The difference in severity may relate to differences in amount of ingested toxin, differential absorption, differential affinity for nerve tissue receptors, or variations in host susceptibility. Type A toxin has been reported to have a greater affinity for tissue receptors \( (19) \).

Although acute gastrointestinal symptoms have been reported to be associated with types B and E botulism \( (1, 4, 7) \), symptoms of nausea, vomiting, or diarrhea occurred early in the illness as frequently with type A as with type B disease. Patients with type A botulism were more likely to have dysarthria, blurred vision, dyspnea, diarrhea, sore throat, and dizziness. Physical findings more often associated with type A disease included arm weakness, ptosis, extraocular muscle palsies, facial nerve dysfunction, tongue weakness, and nystagmus. Patients with type B botulism were more likely to have pupillary...
abnormalities at initial examination and were more likely to have facilitation during rapid repetitive stimulation. Patients who died were older than those who survived. Deaths during the first 2 weeks resulted from cardiorespiratory arrest or infection. Because no deaths occurred before physician contact, improved recognition of the disease may decrease mortality. The lower mortality rate in patients who had elective intubation suggests that early intubation for patients with impaired vital capacities may be indicated. The three late deaths were all related to malfunction of ventilators, emphasizing the need for meticulous respiratory care for patients with respiratory failure in a well-equipped intensive care unit.

ACKNOWLEDGMENTS: The authors thank the many state epidemiologists, state laboratory directors, and private physicians who reported suspected botulism cases to CDC; former Epidemic Intelligence Service officers John M. Boyce, M.D., and Mickey S. Eisenberg, M.D., who reviewed medical records in some of the cases; Ms. Loretta McCroskey and Dr. Charles Hatheway of the Anaerobe Section, Enterobacteriology Branch, Bacteriology Division, Center for Infectious Diseases, CDC, who did much of the diagnostic laboratory work; Robert A. Pollard, M.A., for statistical advice; Ms. Ruth C. Greenberg and Ms. Peggy Hutton for assistance in preparation of the manuscript; and Marcus A. Horwitz, M.D., Roger A. Feidman, M.D. and John V. Bennett, M.D., for their helpful suggestions during preparation of the manuscript.

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Outbreak of Type A Botulism and Development of a Botulism Surveillance and Antitoxin Release System in Argentina

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Botulism is a potentially fatal, neuroparalytic illness resulting from toxins produced by the bacterium Clostridium botulinum. Human illness occurs as infant botulism, botulism from intestinal colonization and wound infections, and foodborne botulism. Symptoms appear approximately 12 to 36 hours after toxin exposure beginning with bulbar and autonomic nervous system disturbances. Descending, symmetrical skeletal muscle weakness, paralysis, and respiratory failure may also follow, which require prompt, supportive therapy including mechanical ventilation.

Botulism antitoxin, the only specific therapy available to ameliorate illness, can help prevent progression of paralysis, reduce duration of illness, and decrease fatality rates.

Supportive care and prompt administration of antitoxin have reduced mortality in the United States to less than 10%, and prompt identification of suspect food vehicles during outbreaks has prevented additional cases and reshaped our understanding of the epidemiology of botulism. Global antitoxin supplies are limited and antitoxin has been unavailable for immediate use in several recent outbreaks (eg, Italy and Egypt). In the United States, the Centers for Disease Control and Prevention (Atlanta, GA) established a rapid-response botulism surveillance and antitoxin release system in 1998.

Context Botulism is an important public health problem in Argentina, but obtaining antitoxin rapidly has been difficult because global supplies are limited. In January 1998, a botulism outbreak occurred in Buenos Aires.

Objectives To determine the source of the outbreak, improve botulism surveillance, and establish an antitoxin supply and release system in Argentina.


Main Outcome Measure Occurrence of botulism and implication of a particular food as the vehicle causing this outbreak.

Results Nine (43%) of 21 bus drivers developed botulism, presenting with gastroenteritis, symptoms of acute cranial nerve dysfunction including ptosis, dysphagia, blurred vision, and motor weakness. One driver experienced respiratory failure. Type A toxin was detected from 3 of 9 patients’ serum samples. All drivers received botulism antitoxin; there were no fatalities. Consumption of matambre (Argentine meat roll) was significantly associated with illness. Among 11 persons who ate matambre, 9 developed illness, compared with none of those who did not eat it (P < .001). The matambre had been cooked in water at 78°C to 80°C for 4 hours, sealed in heat-shrinked plastic wrap, and stored in refrigerators that did not cool adequately. Subsequently, a botulism surveillance and antitoxin release system was established.

Conclusions Insufficient cooking time and temperatures, storage in heat-shrinked plastic wrap, and inadequate refrigeration likely contributed to Clostridium botulinum spore survival, germination, and toxin production. A rapid-response botulism surveillance and antitoxin release system in Argentina should provide more timely distribution of antitoxin to patients and may serve as a model for other nations.

JAMA. 1999;281:1334-1338, 1340 www.jama.com

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ters for Disease Control and Prevention (CDC) maintains surveillance of botulism cases and operates an antitoxin release system. This system depends on a centralized, 24-hour emergency-response telephone number for the release of antitoxin throughout the country and is coordinated at federal, state, and local levels to identify suspected food items and prevent additional cases. The CDC manages a stock of antitoxin and distributes it for emergency use domestically and in member nations of the Pan-American Health Organization.11

Foodborne botulism most commonly occurs following the ingestion of improperly canned or preserved foods that contain preformed toxin.12,13 For foodborne botulism to occur, C. botulinum spores must be present in the food and these spores must survive processing. The food or its packaging must provide an environment suitable for spores to germinate and produce toxin, and finally, persons must consume the food without heating it to temperatures sufficient to destroy the heat-labile C. botulinum toxin.5

An environment favorable to C. botulinum may occur when foods are preserved by inexperienced persons, when faulty equipment is used, or when a contaminated product not intended for long-term preservation is mishandled or packaged in a manner that permits spores to germinate. New vacuum-packaging techniques including sous vide and heat-shrunk plastic wrap have raised concern about the possibility of botulism occurring from foods packaged in these reduced oxygen environments2,14,15; however, few published data on this risk exist.

On January 13, 1998, an infectious diseases physician in a Buenos Aires hospital observed 2 men presenting with ptosis, diplopia, dysphagia, and respiratory difficulties and notified the Directorate of Epidemiology of the Argentine Ministry of Health about a possible botulism outbreak. Both men were bus drivers for the same company who drove the same route and morning shift. Health officials identified 5 other drivers from the same company and shift who also had neurologic signs consistent with botulism. Initial reports suggested that all the drivers had eaten at a home located on the bus route where the drivers stopped during their breaks.

Epidemiologists from the Argentine Ministry of Health called the Foodborne and Diarrheal Diseases Branch, National Center for Infectious Diseases, at the CDC to report the outbreak and request botulism antitoxin to treat these patients and possibly others exposed to an unknown contaminated food source. In this article, we report the outbreak investigation and discuss how the preparation, storage, and packaging of the implicated food may have permitted C. botulinum spores to germinate.

In addition to investigating the outbreak and reviewing the epidemiology of botulism in Argentina, the Argentine Ministry of Health and the CDC used this opportunity to establish a local system for botulism surveillance and antitoxin distribution. The goals of the system are to reinforce surveillance, to deliver antitoxin to patients in Argentina more rapidly and efficiently, and to serve as a model for other nations.

METHODS

Case Identification and Cohort Study

To identify cases, all employees of the bus company with the ill drivers were contacted. Hospitals in the areas of Buenos Aires where cases occurred and where a suspected food was produced were asked to report any patients with acute neurologic illness that could be botulism. Additionally, the outbreak was reported by the local news media. We conducted a cohort study among bus drivers who were ill and also those who were well who drove the morning shift of the bus route. On January 18-19, 1998, we conducted face-to-face interviews and administered a written questionnaire to the drivers. We asked drivers about demographic characteristics, symptoms, and food exposures during the probable exposure period. We defined a confirmed case of botulism as a serum or stool sample that demonstrated botulinum toxin or yielded C. botulinum from a bus driver on the morning shift who ate or drank at the home terminal stop between January 3 and 7. Probable illness was defined as acute cranial nerve dysfunction in this group of drivers during this period. We excluded drivers from other shifts because none reported illness and they did not eat at the terminal stop or share any other common food exposures with the morning shift drivers.

Data were analyzed and relative risks with Fisher exact P values and 95% confidence intervals were calculated using Epi Info version 6.04a (Centers for Disease Control and Prevention, Atlanta, Ga) and Exact Software (the Netherlands).10 Values of P<.05 and 95% confidence intervals that did not include 1 were considered significant.

Environmental Investigation

We interviewed the family living in the house where the drivers ate, asked what foods and drinks were served, and inspected the food preparation and storage facilities. We also inspected the supermarket where the foods were purchased and the facility where a suspected food was produced.

Microbiologic Investigation

Serum specimens were collected from all patients between January 13 and 16, and stool specimens were obtained from patients between January 18 and 20 for both toxin and culture testing for C. botulinum. Assays were conducted in the diagnostics and food laboratory for botulism of the Instituto Nacional de Enfermedades Infecciosas, Buenos Aires. Approximately 10 to 40 g of patients’ feces with an equivalent volume of diluent gelatin were ground in sterile mortars. The solution reposed for 12 to 18 hours at 4°C to allow any toxin present to transfer into the liquid medium. It was then centrifuged at 12 000 rpm for 20 minutes.

Toxicity and neutralization assays were conducted in duplicate using white mice weighing 18 to 20 g. For each mouse, 0.1 mL of monovalent an-
with Botulism

**Table 1. Symptoms of Patients (n = 9) With Botulism**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptosis</td>
<td>9</td>
</tr>
<tr>
<td>Dry mucous membranes</td>
<td>8</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>7</td>
</tr>
<tr>
<td>Blurry vision</td>
<td>7</td>
</tr>
<tr>
<td>Diplopia</td>
<td>4</td>
</tr>
<tr>
<td>Upper extremity weakness</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory difficulty</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
</tr>
<tr>
<td>Stomach pain</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
</tr>
</tbody>
</table>

Toxin presence was confirmed, isolation of *C. botulinum* was attempted on a solid egg-yolk medium.

**RESULTS**

**Case Identification and Cohort Study**

In total, 27 bus drivers worked the same route and shift; all were men. Of these, 22 were interviewed. The other 5 were unavailable for interviews, but either family members or the bus company reported that they were well. One driver, who was not ill, denied eating or drinking anything at the home and was excluded from further analysis. The 21 drivers reported that the home terminal stop was the only location where they had eaten together between January 3 and 7. Local hospitals and health departments did not identify other cases of botulism during this period.

Nine of the 21 bus drivers had illness meeting the case definition for botulism. Three of these patients were confirmed cases and 6 were probable cases. Their median age was 42 years (range, 23–54 years). Seven experienced gastroenteritis 12 to 48 hours after eating food from the terminal stop between January 3 and 5. Two patients were originally hospitalized for severe vomiting and abdominal pain. Reported onset of neurologic symptoms occurred between January 5 and 15 (5-day median incubation period; range, 0–10 days) (FIGURE). All 9 patients reported experiencing ptosis. Neurologic and gastrointestinal symptoms are listed in TABLE 1. One patient experienced respiratory insufficiency and required mechanical ventilation. Trivalent botulism antitoxin (anti-A, B, and E) (Connaught Laboratories Inc, Swiftwater, Pa) was administered to all patients on arrival at the infectious diseases hospital (January 13–15). There were no fatalities.

Among foods consumed between January 3 and 7, only *matambre*, a traditional meat roll prepared from meat, vegetables, spices, and eggs, was significantly associated with illness. Among those who ate the *matambre*, 9 of 11 became ill, compared with none of 10 who did not eat it (relative risk, undefined; 95% confidence interval, 4.37–∞; *P* < .002). No other foods, including solid ham, processed ham, and hot dogs, were significantly associated with illness (TABLE 2).

**TABLE 2**

| Table 2. Probable Dates of Exposure to *C. botulinum* Type A Infection Among Patients With Botulism. |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| January 1998                                     | 1                                                | 2                                                | 3                                                | 4                                                | 5                                                | 6                                                | 7                                                | 8                                                | 9                                                | 10                                               | 11                                               | 12                                               | 13                                               | 14                                               | 15                                               |
| Number of Patients                               | 1                                                | 0                                                | 0                                                | 1                                                | 1                                                | 1                                                | 2                                                | 1                                                | 3                                                | 1                                                | 4                                                | 1                                                | 5                                                | 1                                                | 3                                                | 1                                                |

**Environmental Investigation**

The terminal stop was identified as a home used by the drivers as a resting point and a place to eat while they awaited their scheduled time to resume driving. Although the home was not formally equipped as a restaurant, the owners provided the bus drivers with meals. The drivers and occasionally the homeowner and his family were the only persons who consumed these meals. Perishable foods, including the *matambre*, were kept in 2 large refrigerators inside the home. Although the refrigerators were set at the coldest possible settings, temperatures measured inside the refrigerators were 9°C and 10°C.

The homeowner reported the most recent *matambre* served at the home weighed approximately 4 kg. It had been purchased on January 3, was cut into about 15 slices, and was served in sandwiches to the drivers between January 3 and 6. No other condiment or ingredients were added to the sandwiches. Only this *matambre* was served at the home during the period when persons became ill. No *matambre* remained in the home at the time of inspection.

The implicated *matambre* was brought to a local market where it had been stored in a refrigerator. The market had no temperature records or sales receipts; however, we discovered from customers that *matambres* had recently been sold at reduced prices because of power outages.
The market purchased matambres from a small-scale, commercial producer who made matambres and processed hams at his home. To make matambre, the producer placed a slab of raw beef (1- to 3-cm thick) on a stainless steel table. Ingredients included raw sliced carrots, hard-boiled eggs, salt, red pepper flakes, dried oregano, and commercial potato flour. The meat was rolled up around the vegetables and eggs to make an approximately 10- × 30-cm cylinder. This meat roll was placed into a rectangular stainless steel pan to keep ingredients inside during cooking. Between 10 and 15 matambres in individual steel pans were immersed together into water heated to 78°C to 80°C (never boiling), and cooked for approximately 4 hours. After cooking, the water was drained and the producers reported they checked each matambre to ensure an internal temperature of about 68°C. The producer placed each warm matambre in heat-shrinked plastic wrap, squeezed out the air, and sealed the plastic with heat. The plastic-wrapped matambres were allowed to cool, placed in a walk-in refrigerator, and were stored for up to 2 weeks before being sold to either supermarkets or directly to consumers. The producer reported making matambres every 2 weeks in batches of 15 to 20 each time; the last batch produced before the outbreak was made in early December. The producer was unable to provide receipts or a distribution list with names of locations where his products were sold. He reported that most of his clients distributed his products in the western greater Buenos Aires area. After an inspection by local food safety officials, the facility was closed.

Laboratory Investigation

The mouse assay for botulism toxin presence was performed with serum from each patient; 3 were positive for toxin type A. None of the stool cultures yielded C. botulinum. No implicated matambre was available for testing.

COMMENT

We reported an outbreak of botulism among bus drivers in Buenos Aires, Argentina, caused by consumption of matambre, a food that has not been described previously as a vehicle for botulism. A cohort study determined that all ill persons ate slices of a single matambre; no other foods were associated with illness. Type A toxin was identified from 3 of 9 patients’ serum samples. Unfortunately, no implicated matambre was available for laboratory analysis.

Although consumption of matambre is an established tradition in Argentina, it is usually consumed fresh and is not generally intended for pickling or long-term preservation. Matambres produced by licensed, commercial facilities use nitrates, acidifiers, or other preservatives to prevent bacterial growth; the implicated matambre lacked these. Insufficient cooking, vacuum packaging in heat-shrinked plastic wrap, and inadequate refrigeration may have provided conditions for live spores to germinate and produce toxin. To our knowledge, this is the first time heat-shrinked plastic wrap has been linked to botulism, emphasizing concern about the safety of this packaging method.

The matambre that is believed to be the cause of this outbreak was cooked at relatively low temperatures (78°C-80°C) over a time period (approximately 240 minutes) too short to kill all C. botulinum spores. These spores are difficult to destroy using conventional cooking techniques; temperature survival curves have demonstrated C. botulinum survival at 80°C for more than 270 minutes. In fact, a nonkilling heat shock and the lack of preservatives or acidifiers may enhance germination and toxin elaboration by C. botulinum spores. To safely prepare foods intended for canning or long-term storage, the US Department of Agriculture recommends that all low-acid foods (foods with pH >4.6, including red meats, seafood, poultry, milk, and fresh vegetables) be sterilized at temperatures of 116°C to 121°C in pressure canners operated at 0.68 to 0.97 atm (10-15 lb/in²). At these temperatures, the time needed to destroy bacteria in low-acid canned food ranges from 20 to 100 minutes. The exact time depends on the kind of food being canned, the way it is packed, and the amount of food being cooked. The time needed to safely process low-acid foods in boiling water canners ranges from 7 to 11 hours. The time and temperatures used to cook the matambre in this outbreak were insufficient to kill all botulism spores.

Reduced oxygen packaging of foods can increase the risk of certain foodborne illnesses if other safety barriers have not been applied. Although vacuum packaging may inhibit the growth of some types of bacteria in foods, several Clostridium species can grow and produce toxin in this environment. To reduce the risk of botulism from foods in reduced oxygen packaging, the US Food and Drug Administration requires documented employee training in plants that use reduced oxygen packaging, stringent refrigeration, specific labeling with storage temperature instructions and use-by dates, and plant approval for reduced oxygen packaging of fish, soft cheeses, meats, and poultry.

Table 2. Foods Consumed by Bus Drivers (n = 21) in Buenos Aires, Argentina, in January 1998*

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Ate Food</th>
<th>Did Not Eat Food</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matambre</td>
<td>9/11 (82)</td>
<td>0/10 (0)</td>
<td>Undefined (4.37–∞)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Bologna</td>
<td>1/1 (100)</td>
<td>8/20 (40)</td>
<td>2.50 (1.46–4.28)</td>
<td>.43</td>
</tr>
<tr>
<td>Salt</td>
<td>1/1 (100)</td>
<td>8/20 (40)</td>
<td>1.30 (0.49–3.45)</td>
<td>.67</td>
</tr>
<tr>
<td>Hot dog</td>
<td>1/2 (50)</td>
<td>8/19 (42)</td>
<td>1.19 (0.27–5.23)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Salad</td>
<td>1/2 (50)</td>
<td>8/19 (42)</td>
<td>1.19 (0.27–5.23)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Solid ham</td>
<td>2/5 (40)</td>
<td>7/16 (44)</td>
<td>0.86 (0.26–2.85)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Processed ham</td>
<td>2/5 (40)</td>
<td>7/16 (44)</td>
<td>0.86 (0.26–2.85)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

*Matambre is the traditional meat roll in Argentina and mate is green tea.
The matambre in this outbreak was packaged in a reduced oxygen environment and lacked other safety barriers needed to prevent Clostridium spores from proliferating.

Inadequate refrigeration also provided a favorable growth environment for C. botulinum. The refrigerators (at temperatures between 9°C-10°C) used to store the matambre at the terminal stop were not cold enough for safe storage of perishable foods.18,23 The US Food and Drug Administration recommends that refrigerator temperatures be 5°C or colder to prevent the growth of C. botulinum in foods stored in reduced oxygen packaging.15 Maintenance of adequate storage temperatures for the matambre also was not documented by the producer or the market where it was sold.

The clinical characteristics of botulism among patients in this outbreak differed in several respects from those in other reports.1,3,4 Typically, most patients with botulism develop severe muscular weakness and mild gastroenteritis. In this outbreak, the majority of patients experienced severe gastroenteritis, and only 1 patient developed severe muscular paralysis. In US cases of type A botulism, the reported median incubation period was 1 day (range, 0-5 days).3 In the Argentine outbreak, the incubation period was longer; the median time between food exposure and onset of neurologic symptoms onset was 5 days (range, 0-10 days). Several reported outbreaks of botulism from Europe have described patients with primarily mild to moderate symptoms, but most of these outbreaks have been caused by type B toxin.24-26 It is not known why some strains of C. botulinum cause milder illness than others, although the number of spores present and amount of toxin produced and ingested may influence clinical manifestations. The severity of gastroenteritis experienced by these patients could have also occurred if the matambre had been contaminated by other bacteria or toxins.

The outbreak investigation had several limitations. All of the implicated matambre had been consumed and all remaining matambres from the supermarket where the implicated meat was purchased were discarded before the investigation began. Although no matambres were available for laboratory analysis, epidemiologic data and information gained from the investigation implicated the product. Furthermore, receipts were unavailable from the supermarket or the matambre producer to document dates of purchase or exact distribution of the product. However, no additional cases of type A botulism were detected.

The use of heat-shrunked plastic wrap and vacuum packaging for cooked foods followed by inappropriate refrigeration may provide an ideal environment for the growth of C. botulinum, and the safety of these packaging methods should be further investigated. Education of food manufacturers and distributors, including the importance of adequate cooking time and temperatures to kill C. botulinum spores, adding acidifiers or preservatives to foods intended for prolonged shelf life and refrigerating foods properly, may help prevent such outbreaks.

Enhancing Surveillance and Establishing an Antitoxin Release System

Botulism is an important public health problem in Argentina. Data maintained by the Argentine Ministry of Health indicate that during the years 1979-1997, 277 cases of botulism were reported in Argentina (Ministry of Health, Republic of Argentina, unpublished data, 1998). Between 1987 and 1997, the CDC released 54 vials of antitoxin to Argentina (CDC, unpublished data, 1998). In 1997, 23 patients with suspected foodborne botulism were reported in Argentina, about the same number of laboratory-confirmed cases per year as in the United States,27 which has a population approximately 10 times that of Argentina. In addition, 11 cases of culture-confirmed infant botulism were reported in Argentina that year. Only 1 case of wound botulism has been described in Argentina. Of 89 laboratory-confirmed cases reported between 1991 and 1997, 83 (93%) were identified as toxin type A, 4 (5%) as toxin type E (all occurred in a single outbreak), and 2 (2%) as toxin type B (Ministry of Health, Republic of Argentina, unpublished data, 1998). In the United States, toxin types A, B, and E were identified in 60%, 30%, and 10% of cases, respectively.3,8,27

Previous outbreaks in Argentina have been caused primarily through the consumption of improperly preserved vegetables and meats. Although C. botulinum spores are ubiquitous, they are found most frequently in soil samples. The level of Clostridium species contamination on vegetables, particularly those harvested directly from soil, is generally higher than that found in meats2 and may in part explain why preserved vegetables are more frequently implicated.

Because of the relatively high incidence of botulism in Argentina, the Ministry of Health and the CDC collaborated to establish, in January 1998, an antitoxin release and surveillance system for botulism in Argentina based on the US program. The system components include (1) establishment of a local stock of antitoxin, (2) a mechanism for antitoxin distribution within Argentina, (3) emergency notification and response for suspect cases, and (4) laboratory confirmation of suspect cases. The critical element that ensures both rapid response and effective surveillance is the maintenance of a centralized antitoxin supply and a single emergency release telephone number. The system is briefly described below.

Antitoxin Supply. Botulism antitoxin was supplied to Argentina through a modification of the existing agreement between Pan-American Health Organization and the CDC. Ultimately, the Argentine Ministry of Health may contract directly for botulism antitoxin from pharmaceutical manufacturers. Such a contract would guarantee annual supply of product and would simplify maintenance of Argentina’s antitoxin supply. The emergency stock is currently maintained by the Ministry of Health.

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Antitoxin Distribution. Patients with suspected botulism are identified based on clinical signs and symptoms, food history, and supportive data from ancillary diagnostic testing. Reporting of cases initiates the process of antitoxin release. To request antitoxin, treating physicians or provincial epidemiologists consult with an epidemiologist at the Directorate of Epidemiology at the National Ministry of Health using a 24-hour emergency telephone number. The epidemiologist from the Ministry of Health obtains information from the treating physician using a botulism case report form, requests a copy of the patient’s medical chart, and requests that diagnostic specimens be submitted to the laboratory. Consultation between treating physicians and the Ministry of Health epidemiologist may assist in differentiating botulism cases from other illnesses, thus preventing unnecessary antitoxin administration. If the epidemiologist and treating physician determine that botulism is a likely diagnosis, the epidemiologist arranges the release of 10-mL vial of antitoxin for each patient.

Emergency Notification and Response. To ensure investigation of potential additional cases of botulism, the epidemiologist at the Ministry of Health who receives a request for antitoxin notifies provincial health authorities by telephone. Inspection of the patient’s home and/or investigation of suspected food vehicles are then initiated. The epidemiologist also alerts national food safety authorities to assist with commercial product recalls if necessary or if the vehicle is unknown.

Laboratory Confirmation. Ministry of Health epidemiologists will provide physicians and provincial epidemiologists with information about specimen collection and will direct specimens to laboratory confirmation and surveillance for botulism. The system also improves coordination between public health authorities and food safety agencies to facilitate investigation of outbreaks and prevent additional cases, and it provides a mechanism to track changes in the epidemiology of the disease.

The adoption of this system by Argentina serves as a model for other nations. Centralized antitoxin release, tightly linked to preventive measures and surveillance, provides an effective mechanism for managing this rare but deadly disease. In addition, the creation of a cooperative, rapid-response botulism surveillance network may provide a useful framework for a future surveillance system to monitor the emergence of new and resurgent infectious diseases throughout the world.

Acknowledgment: We thank Norma Binzstein, MS, Lorretta McCroskey, MT, and Silvina Ancieri for their collaboration.

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Outbreaks of Gastrointestinal Illness of Unknown Etiology Associated with Eating Burritos -- United States, October 1997-October 1998

From October 1997 through October 1998, 16 outbreaks of gastrointestinal illness associated with eating burritos occurred in Florida, Georgia, Illinois, Indiana, Kansas, North Dakota, and Pennsylvania. All but one outbreak occurred in schools, and most of the approximately 1700 persons affected were children. This report summarizes investigations of two of these outbreaks and describes the collaborative efforts of CDC, the U.S. Department of Agriculture (USDA), and the Food and Drug Administration (FDA) to identify the etiologic agent(s); these outbreaks may have been caused by an undetected toxin or a new agent not previously associated with illness.

Georgia

On March 23, 1998, the Hall County Health Department received a report that students in an elementary school became ill after eating lunch. Health officials obtained food and illness histories from 452 (77%) of the 584 students. A case was defined as nausea, abdominal cramps, vomiting, or diarrhea within 24 hours in a person after eating the school lunch on March 23. Of the 452 students, 155 (34%) had illnesses meeting the case definition. Symptoms most commonly reported were nausea (89%), headache (65%), abdominal cramps (53%), vomiting (29%), and diarrhea (17%). The median incubation period was approximately 15 minutes (range: 5-25 minutes), and median duration of illness was 4.5 hours (range: 10 minutes-8 hours).

The children had access to nine foods during lunch. One hundred forty-five (48%) of 304 who ate burritos, and 10 (7%) of 148 who did not eat burritos became ill (relative risk {RR}=7.1; 95% confidence interval {CI}=3.8-13.0). The burritos were produced by company A; the main ingredients were beef, chicken, pinto beans, seasoning, textured vegetable protein, and tortillas.

Florida

On October 8, 1998, the Hillsborough County Health Department was notified that students at 12 elementary schools became ill after eating lunch. Health officials conducted investigations at two schools. A case was defined as nausea, abdominal cramps, or vomiting in a person after eating the school lunch on October 8. In both schools, students who initially reported illness and classmates in the three classes with the highest number of cases were interviewed. Twenty-seven cases were identified. The predominant symptoms of the 14 ill children identified in one school were abdominal cramps (88%), vomiting (62%), headache (62%), and nausea (39%). In the other school, symptoms among the 13 identified ill children were abdominal cramps (82%), vomiting (55%), headache (27%), nausea (18%), and dizziness (18%).

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In a case-control study at one school, eight (57%) of 14 case-patients and five (13%) of 38 well children ate burritos (odds ratio [OR]=8.8; 95% CI=1.8-47.6). In the other school, 11 (85%) of 13 case-patients and 11 (33%) of 33 well children ate burritos (OR=11.0; 95% CI=1.8-87.6). The tortillas used to make the burritos were supplied by company B; the fillings, beef at one school and beef and pinto beans at the other, were made in the two school kitchens.

Summary Findings

During October 1997-March 1998, burritos from three outbreaks of gastrointestinal illness were traced to company A, and during May-October 1998, burritos from another 13 outbreaks were traced to company B. Three outbreaks were linked to chicken and bean burritos, pork-sausage and egg burritos, and beef burritos; the other 13 were linked to beef and pinto bean burritos. All burritos used tortillas made with wheat flour. The burritos were distributed frozen and prepackaged except in Florida, where the filling was prepared locally.

The major symptoms were nausea, headache, abdominal cramps, and vomiting, typically beginning within 60 minutes after eating a burrito and lasting less than 24 hours. No one was hospitalized.

USDA requested that both companies A and B initiate timely national recalls, and approximately 2 million lbs of burritos were recalled or withheld from distribution. Company A and its tortilla supplier were unrelated to company B and its supplier.

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Editorial Note

Editorial Note: Data from the two outbreaks described in this report and the other 14 outbreaks indicate that the symptoms, incubation period, and duration of illness were similar. The variations in symptoms in the outbreaks in Florida and Georgia could be associated with differences in case finding methods. Epidemiologic investigations in several of the other outbreaks also have implicated burritos, which consisted of meat or vegetable filling wrapped in a tortilla. Data from the Florida outbreak suggest that the etiologic agent was in the tortillas because the filling was made locally. Outbreaks associated with products made by two unrelated companies that used different tortilla suppliers suggest that the agent was an ingredient common to the products made by both companies. No common first-line suppliers were identified; however, whether the source of any ingredients was shared has not been determined.

The short incubation periods suggest that a preformed toxin or other short-acting agent was the cause of illness. Possible agents include bacterial toxins (e.g., Staphylococcus aureus enterotoxin and Bacillus
cereus emetic toxin); mycotoxins (e.g., deoxynivalenol {DON}, acetyl-deoxynivalenol, and other tricothecenes), trace metals, nonmetal ions (e.g., fluorine, bromine, and iodine), plant toxins (e.g., alkaloids such as solanines, opiates, ipecac, and ergot; lectins such as phytohemagglutinin; and glycosides), pesticides (e.g., pyrethrins, organophosphates, and chlorinated hydrocarbons), food additives (e.g., bromate, glutamate, nitrite, salicylate, sorbate, and sulfite), detergents (e.g., anionic detergents and quaternary amines), fat-soluble vitamins, spoilage factors (e.g., biogenic amines, putrefaction, and free fatty acids), or an unknown toxin. Mass sociogenic illness is an unlikely explanation based on the number of different sites where outbreaks have been reported over a short interval and the link to only two companies.

B. cereus emetic toxin and S. aureus enterotoxin are common causes of food poisoning, but headache is not usually a prominent feature, and most outbreaks traced to these toxins have incubation periods of 2-4 hours, which is longer than observed in these outbreaks (1,2). Food samples from five outbreaks were negative for B. cereus and S. aureus by culture and toxin analysis; testing from these same outbreaks for alkaloids, biogenic amines, and pesticides also did not identify the causative agent.

Some metals, such as cadmium, copper, tin, and zinc, can irritate mucosal membranes and cause gastrointestinal illness after short incubation periods; however, only elemental aluminum was mildly elevated in the burrito samples, and there is no evidence that it causes these symptoms (3,4). Several plant toxins, such as phytohemagglutinin, may survive cooking and cause gastrointestinal symptoms; however, previous outbreaks associated with phytohemagglutinin have been linked to red kidney beans and not pinto beans (5).

Outbreaks with symptoms and incubation periods similar to those described in this report have occurred in China and India, where illness has been linked to consumption of products made with grains contaminated with fungi. These fungi produce heat-stable tricothecene mycotoxins called vomitoxin (6). In China, 35 outbreaks affecting 7818 persons during 1961-1985 were attributed to consumption of foods made with moldy grain (7). Corn and wheat samples collected during two outbreaks had higher levels of DON than those collected at other times. In India in 1987, 97 persons consumed wheat products following heavy rains (8). DON and other tricothecene mycotoxins were detected in the implicated wheat products, and extracted toxins caused vomiting in laboratory tests on puppies (8). High doses of DON are known to cause vomiting in pigs (9). Laboratory testing from burrito samples from some of the U.S. outbreaks in this report detected DON within the acceptable FDA advisory level of 1 ppm for finished wheat products (10). However, the possibility remains that a mycotoxin is the cause.

To facilitate coordination of outbreak investigation and traceback activities, local health departments are encouraged to report immediately any outbreaks characterized by an incubation period of less than 1 hour, duration of less than 1 day, and symptoms including nausea, headache, abdominal cramps, and vomiting regardless of the suspected vehicle through state health departments to CDC. CDC recommends that vomitus, serum, stool, and urine specimens be obtained from at least 10 ill persons, if possible, in each outbreak and that any leftover food samples and shipping containers be saved.

In addition to testing food specimens for specific toxins and agents, laboratories at USDA, FDA, and CDC are examining these specimens by cell culture assays, biologic toxicity assays, and chemical analyses for toxins. The interagency investigating team seeks to collaborate with groups capable of analyzing suspect burritos and tortillas to identify the etiologic agent. Additional information is from CDC’s Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, telephone (404) 639-2206.

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