

## CHAPTER 19

# Botulism as an Intestinal Toxemia

Stephen S. Arnon

Traditionally, botulism has been known as a foodborne disease and as such has always been of interest to gastroenterologists. Eighteen years ago the traditional view of botulism was revised and expanded following the recognition of a new form of the disease, i.e., infant botulism. Infant botulism is an infection of the intestinal tract in which ingested *Clostridium botulinum* spores germinate, multiply, and temporarily colonize the lumen of the large intestine and produce botulinum toxin in it. A minute fraction of the intraluminal toxin is then absorbed and carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly. Clinically, the neuromuscular junction is the most important peripheral cholinergic synapse, and its poisoning by botulinum toxin results in hypotonia and flaccid paralysis. Botulinum neurotoxin is the most poisonous substance known. Its seven serologically distinguishable forms have arbitrarily been given the letters A–G. These seven toxin types serve as convenient clinical and epidemiological markers.

Recognition of infant botulism led to the discovery of two novel clostridial species that can make botulinum-like neurotoxins and colonize the human colon. Discovery of these additional neurotoxic clostridia necessitated a better descriptive term for the infectious form of botulism, now referred to as “the intestinal toxemias of infancy” or “intestinal toxemia botulism.” The distinction from diseases caused by other toxin-producing intestinal bacteria (e.g., *Shigella dysenteriae* type 1, *Escherichia coli*, *Vibrio cholerae*) is that the intestinal toxemia clostridia neither invade the mucosa (like *Shigella* or some *E. coli*) nor produce a mucosally active toxin (like *V. cholerae* or other *E. coli*). Under exceptional circumstances (e.g., changes in normal anatomy and gut flora), adults can become ill with “infant-type” botulism. Intestinal toxemia botulism in infants and adults is the subject of this chapter.

## HISTORY

Reliable descriptions of foodborne botulism date to nineteenth century Germany, where Kerner described an illness known locally as “sausage poisoning.” In 1895 in the small Belgian town of Ellezelles, an outbreak occurred among 34 musicians who had eaten from a raw ham preserved in salt brine. Twenty-three persons became sick, 13 severely, and 3 died. This episode of botulism became famous because Emile van Ermengem (1851–1922), Professor of Microbiology at the University of Ghent, carried out a now classical investigation that established the essential aspects of botulism. van Ermengem discovered the obligatorily anaerobic, spore-forming bacterium known today as *Clostridium botulinum* and its phenomenally potent heat-labile toxin, which caused a wide variety of vertebrate animals to die from flaccid muscle paralysis. Much subsequent work in the United States on the ecology of the bacterium and the eradication of its spores from canned foods was carried out in the early decades of the twentieth century by Meyer, Dack, and colleagues (1).

The second form of human botulism to be recognized, wound botulism, was first reported in 1951 (1). Wound botulism is an infectious disease and is the pathophysiological equivalent of tetanus. Wound botulism remains the rarest form of human botulism, with somewhat over 100 cases reported worldwide. An occasional case of wound botulism has occurred as a complication of intestinal surgery (2). Wound botulism was the subject of a recent review (3) and will not be discussed further here.

Infant botulism, the third form of human botulism, was recognized as a distinct clinical and epidemiological entity in 1976 (4,5), more than 50 years after Orr had first demonstrated the possibility experimentally (6). Shortly after modern recognition of the first cases and the naming of the entity, the novel pathogenesis of infant botulism was demonstrated (7,8). Discovery in the late 1970s of a laboratory-proven case of infant botulism that occurred in 1931, yet was misdiagnosed at the time, helped confirm that infant botulism was not a “new” disease but only a

S. S. Arnon, MD: Infant Botulism Prevention Program, California Department of Health Services, Berkeley, California 94704.

newly recognized one (9). The first case of infant botulism to be caused by type F botulinum toxin was recognized in New Mexico in 1979 (10); later the causative bacterium of this case was found to be a unique strain of *Clostridium baratii* that produced a type F-like botulinum toxin (11,12). The first and thus far only two cases of infant botulism caused by type E toxin were recognized in Rome, Italy in 1986 (13), which resulted in discovery of a unique strain of *Clostridium butyricum* that produced a type E-like botulinum toxin (12,14).

Once the intestinal toxemias of infancy had been recognized, it became apparent that intestinal toxemia botulism could occur in older children and adults under exceptional, nonphysiological circumstances. The first case report that provided impeccable evidence of infant-type botulism in an adult appeared in 1986 (15). To date, recognized intestinal toxemia botulism has resulted from any of the three neurotoxic clostridial species of *C. botulinum*, *C. baratii*, and *C. butyricum*. However, other systemic illnesses presently considered idiopathic may possibly find their explanation in the toxins of the various clostridial species that are capable of colonizing the large intestine, if a search for them is made.

Most recently, botulinum toxin has become celebrated as the first microbial toxin to be harnessed into service as a medicine for the treatment of human disease (16-18). The toxin is used to treat a variety of ophthalmological and neurological conditions characterized by overactivity or spasm of a particular muscle or muscle group (19).

## INFECTIOUS AGENTS

Clostridia by definition are the obligatorily anaerobic, gram-positive, spore-forming rods. Clinical botulism from an intestinal toxemia may be caused by any of three clostridial species that produces either botulinum neurotoxin itself or a closely related botulinum-like neurotoxin. These three species are *C. botulinum* and one unique strain each within the species *C. baratii* and *C. butyricum* (11-14).

In general, each strain of *C. botulinum* produces a single toxin type. However, strains that produce predominantly one toxin type together with a lesser amount of a second toxin type are known and have been given the designations Ab (20), Af (21), Ba (22), and Bf (23). By use of the polymerase chain reaction, it was recently shown that 43/79 (54%) of type A strains examined also carried the gene for type B toxin (24). However, only 1 of these 43 type A strains expressed biologically active type B toxin, thus defining it as an Ab strain. A further remarkable finding was the discovery of the type B toxin gene in two strains of *Clostridium subterminale*, neither of which by bioassay expressed the toxin gene (24). The identification of the gene(s) for botulinum and botulinum-like toxins in an increasing variety of non-*C. botulinum* species suggests that these toxin-encoding genes may await discovery in other clostridial species not yet examined.

The fourth clostridial species known to produce a neurotoxin, *C. tetani*, is apparently unable to colonize the human infant intestinal tract, as least as judged by the absence of reported clinical cases. However, the almost

universal immunization of women in the developed world with tetanus toxoid and the in utero transfer of maternal antibody to the fetus may prevent clinically evident cases of infant intestinal tetanus toxemia from occurring, while in the less developed world, tetanus in infancy is usually ascribed to "tetanus neonatorum." Perhaps tetanus neonatorum cases, especially those 2 months of age and older that lack an obvious wound source of toxin, should be evaluated for the possibility of intestinal colonization by *C. tetani*.

The bacterial species designated as *C. botulinum* is not a homogeneous collection of metabolically similar bacteria. Instead, the species was intentionally created as an aggregate of the strains that produce botulinum neurotoxin. This taxonomic decision preceded by several decades the discovery of the neurotoxic strains of *C. baratii*, *C. butyricum*, and *C. botulinum* type G. *Clostridium botulinum* is subdivided into four groups based on cultural and biochemical criteria. Group I consists of proteolytic strains that produce botulinum neurotoxin types A, B, and F; group II consists of nonproteolytic strains that produce neurotoxin types B, E, and F; group III consists of the strains that produce neurotoxin types C and D; and group IV consists of a single strain that produces neurotoxin type G (1). This latter group was recently proposed for inclusion in a new species, *C. argentinense* (25). In the next few years the nomenclature for all *C. botulinum* strains will probably be revised as ribosomal RNA and DNA hybridization techniques disclose the more correct taxonomic relationships between botulinum neurotoxin-producing strains and their nonneurotoxic clostridial counterparts (26, 26a, 26b).

Seven antigenic variations of botulinum neurotoxins exist and are distinguished from each other by the absence of cross-neutralization by monovalent antitoxins. These seven toxin types have been arbitrarily assigned the letters A-G (1). Because the neurotoxins produced by *C. butyricum* and *C. baratii* can be neutralized by either botulinum type E or type F antitoxin, respectively, these latter neurotoxins are referred to as "botulinum-like." The structural genes for the two botulinum-like toxins have been sequenced; the type E-like toxin has approximately 97% homology to classical botulinum type E toxin (27,28), while the type F-like toxin has approximately 70% homology to classical nonproteolytic type F botulinum toxin (29).

Botulinum toxin is the most poisonous poison known, and tetanus toxin is second only to botulinum toxin in potency (30). The extreme poisonousness of these two toxins derives from their specificity for synaptic neural cells and their enzymatic action that prevents synaptic transmission (see next section). The lethal (bloodstream) dose of botulinum toxin for a human has been estimated by extrapolation from primate and other animal studies to be less than, and perhaps substantially less than, 1 ng/kg (18,31); tetanus toxin is approximately one order of magnitude less potent (30,31).

## PATHOGENESIS AND PATHOPHYSIOLOGY

As presently known, intestinal toxemia botulism results from ingestion of spores of any one of three neurotoxi-