Botulism is a rare but severe disease mainly resulting from food poisoning or intestinal colonization. Food poisoning, including botulism, certainly occurred in ancient times. However, this disease was not recognized as a distinct pathological entity until the latter half of the 18th century. A first detailed description of the clinical symptoms was provided by Kerner in Germany (1815–1817), who investigated numerous cases in southwest Germany resulting from the consumption of blood sausage. The disease was called “sausage poisoning”. Notably, Kerner concluded that a toxin develops in blood sausage under anaerobic conditions that it is lethal at very small doses and induces flaccid paralysis. He speculated that this toxin may have a therapeutic application in suppressing muscle toxicity or hypersecretion of body fluids of neurological disorders manifesting by overactivity. In 1895, van Emmingen identified the causative agent, Bacillus botulinum, later renamed Clostridium botulinum, which he isolated from a ham and from a human who died from botulism during a severe outbreak in Belgium. He found that the culture filtrates administered to experimental animals induce the symptoms of botulism and lead to death. A few years later (1904), Landman isolated a strain from canned beans, which caused a German botulism outbreak. This was a unique event showing that botulism is a disease not only of meats or fish, but also of vegetables. Leuch (1910), from the Royal Institute of Infections in Berlin, found on the basis of the absence of cross-neutralization that the 2 strains produce distinct toxins. From the end of 18th century to the beginning of the 19th century, numerous cases have also been reported in the United States, mainly due to the consumption of heat-treated canned vegetables, which was a novel mode of food preservation at that time. It appeared that the botulinum toxin (BoNT) produced by the American strains differed from that of the European strains. The strains from canned vegetables were designated type A, and those from ham were designated type B [1].

Strains isolated from chickens with botulism in the United States and cattle in Australia were identified as belonging to a novel type, termed type C by Bergston and Seddon (1922). A distinct microorganism was isolated from a bovine with botulism in South Africa by Meyer and Gunnison (1928) and was called type D. In 1934, 2 outbreaks of human botulism caused by the consumption of fish in New York and in the Ukraine were identified as type E by Gunnison et al (1936–1937), because the strains from both of these outbreaks were both antigenically similar and distinct from the previously identified C. botulinum strains. Type F was identified in Langeland, Denmark, in 1958 in specimens from 2 persons who had eaten a homemade liver paste, and C. botulinum type G was isolated in 1970 in specimens of soil in Argentina by Gimenez and Cicarelli [1].

Botulism was first recognized as a result of food poisoning. Other forms of botulism have been identified, such as wound botulism in 1940–1945, and botulism by intestinal colonization with neurotoxigenic strains in young infants (infant botulism) in 1976 [2] and later in adults [3]. Arnon and colleagues have investigated numerous cases of infant botulism, which is currently the prevalent form of botulism in the United States, and have developed a therapy based on human immune globulins [4, 5].

The taxonomic position of C. botulinum was originally based on 1 phenotype—the production of a BoNT—whereas the nontoxic variant strains were assigned to different species, such as Clostridium sporogenes and Clostridium subterminale. Subsequently, physiological differences...
between *C. botulinum* strains were identified, and the species was divided into 4 physiological groups [6]: group I, consisting of *C. botulinum A* and proteolytic strains of *C. botulinum B* and F; group II, consisting of *C. botulinum E* and nonproteolytic strains of *C. botulinum B* and F; group III, consisting of *C. botulinum C* and D; and group IV, consisting of *C. botulinum G*.

The latter group is metabolically distinct from the other groups and has been assigned to a different species, called *Clostridium argentinense*. Since then, neurotoxigenic strains belonging to different *Clostridium* species, such as *Clostridium butyricum* and *Clostridium baratii*, have also been characterized and are now assigned to group V and VI, respectively. Generally, 1 strain of *C. botulinum* produces 1 type of BoNT, but strains synthesizing a combination of BoNT types (bivalent strains Ab, Ba, Af, and Bf) have been observed [7].

Therefore, on the basis of their immunological properties, BoNTs were classified into 7 toxinotypes (A to G). However, all these toxins develop similar pathological effects consisting primarily of flaccid paralysis. Each toxinotype uses different ways to block neurotransmitter release. Indeed, BoNTs recognize distinct protein receptors (synaptic vesicle protein SV2 isoforms for BoNT/A, BoNT/E, and BoNT/F and synaptotagmin 1 and 2 for BoNT/B and BoNT/G [8]), in addition to gangliosides GD1α/GT1b, to target neurons and cleave one of the 3 proteins (VAMP, SNAP25, or syntaxin) of the SNARE complexes, which are key players in the evoked release of neurotransmitter. BoNT/A and BoNT/E cleave SNAP25; BoNT/B, BoNT/D, BoNT/F, and BoNT/G are specific proteases of VAMP; and BoNT/C recognizes both SNAP25 and syntaxin. Although several BoNTs share the same substrate, each toxinotype uses a unique cutting site [9, 10].

Systematic DNA sequencing of *bont* genes and *C. botulinum* genomes demonstrated an increased diversity of BoNT molecules. Each toxinotype is divided into subtypes (BoNT/A1-5, BoNT/B1-5, BoNT/E1-8, BoNT/F1-7, mosaic BoNT/CD, and BoNT/DC), which differ by 2.6%–31.6% at the amino acid level. These differences can affect the binding and neutralization potency by monoclonal and polyclonal antibodies and also the affinity and catalytic efficiency of BoNTs for their substrate [7]. Recently, Arnon and colleagues identified a *C. botulinum* strain that contains 3 *bont* gene clusters consisting of BoNT subtypes A2, F4, and F5 [11].

In the 2 companion articles in the current issue of the *Journal of Infectious Diseases* [12, 13], Arnon and colleagues report the characterization of a novel toxinotype, called BoNT/H, on the basis of sequence analysis and the absence of cross-neutralization with sera against the previously identified BoNT types. This is the first new toxinotype described in >40 years. BoNT/H is produced by a new bivalent strain from group I, which predominantly synthesizes BoNT/B.

BoNTs constitute a set of diverse toxic molecules, produced by diverse bacteria, that enter specific neuronal cells via different receptors and target diverse substrates but focus on the blockade of the same physiological pathway, neuroexocytosis. Indeed, BoNTs are the most potent inhibitors of neurotransmitter release in man and animals. Does this diversity reflect an adaptation of neurotoxigenic clostridia to specific hosts? BoNT/A, BoNT/B, BoNT/E, and, to a lesser extent, BoNT/F are most frequently involved in human botulism; BoNT/C is most common in birds; and BoNT/D is most common in cattle. Does BoNT/H correspond to additional host specificity or to a distinct geographical distribution? The bivalent BoNT/Bh strain described by Arnon et al has been isolated from an infant with botulism, and the diversity of *C. botulinum* types in infant botulism seems to reflect the geographic distribution of spores in the environment. However, the discovery of a novel type, such as BoNT/H, forces us to update methods for detection of and specific therapy for botulism. Moreover, BoNT/H may also represent an additional potential therapeutic tool because BoNTs, notably BoNT/A, are widely used today in numerous medical indications.

**Notes**

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**References**


