

# The story of *Clostridium botulinum*: from food poisoning to Botox

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**ABSTRACT** – In the last fifty years, *Clostridium botulinum* has become notorious for its ability to produce the deadly botulinum neurotoxins. While botulinum toxin A, better known as Botox™, is universally recognised by the public as a cosmetic enhancement tool, the botulinum neurotoxins are commonly used off-label for many medical conditions in ophthalmology, neurology and dermatology. The versatility of these botulinum toxins has made *Clostridium botulinum* one of the most widely known bacterial pathogens in medical history. This article outlines the discovery of botulinum toxins through to their present day applications in medicine.

**KEY WORDS:** botulinum toxin, dermatology, food poisoning, human disease, neurology, ophthalmology

## The botulinum toxins

*Clostridium botulinum* is a rod-shaped, gram-positive anaerobic bacterium. Each of the seven serotypes of this bacterium (A, B, C, D, E, F and G) produce a unique form of botulinum neurotoxin (also designated A to G).<sup>1,2</sup> Types A, B and E are commonly involved in human botulism<sup>3</sup> and found in terrestrial, marine and fresh water environments.

Botulinum toxin A, produced by the high yield Hall strain of *C botulinum*, is the most potent form of botulinum neurotoxin.<sup>4</sup> Botulinum toxin is a high

molecular weight protein of 150,000 daltons with noncovalent proteins that protect it from digestive enzymes, thereby making it a highly dangerous food poison. The toxin is destroyed by heating at 80°C for at least one minute.

Botulinum toxin A is widely distributed and commercially available as Botox™ (Allergan, Inc) in North America while Dysport™ (Speywood, UK) dominates the European markets. Botulinum toxin B is marketed as Myobloc (Elan Pharmaceuticals) in the USA and Neurobloc (Elan Pharmaceuticals) in Europe; both are currently under review by the US Food and Drug Administration (FDA).<sup>5,6</sup> The FDA specify that Botox™ be distributed in vials of 100±30 mouse units (U) with 1 U equal to the median amount necessary to kill half the sample of mice (LD<sub>50</sub>).<sup>2,4</sup> Of further note, 1 U of Botox™ is equivalent to 3 ng of botulinum toxin A or 2–5 U Dysport™ (the latter will not be further discussed in this essay).<sup>2</sup> Depending on the medical condition, 30–300 U (1–10 ng) Botox™ injections are required two to six times per year, and administration of the toxin at higher concentrations or too frequently creates the risk of developing antibodies that nullify any beneficial effects.<sup>2</sup> As a pharmaceutical, botulinum toxin A has a large margin of safety with an LD<sub>50</sub> of 3,000 U (100 ng) in humans and side effects from treatment are minimal.

All botulinum toxins have a similar mode of action whereby they interfere with the transmission of nerve impulses by inhibiting the release of the acetylcholine neurotransmitter from nerve terminals at the neuromuscular junction. The effect is long lasting but also reversible, as new nerve terminals sprout to replace the formerly inhibited ones.<sup>7,8</sup>

## Food poisoning from botulinum toxins

In the late 1700s, botulism, a disease caused by human ingestion of botulinum toxins in contaminated foods, led to many deaths in Europe. Economic poverty caused by the Napoleonic War (1795–1813) led to the neglect of sanitary measures in rural food production. The primary source of botulism was smoked blood sausages. By 1811, the Department of Internal Affairs of the Kingdom of Württemberg attributed 'sausage poisoning' to a substance named

## Key Points

*Clostridium botulinum* has become one of the most notorious bacteria in history because of its ability to produce the deadly botulinum neurotoxins

Botulinum toxin, once a food poison and later exploited as a biological weapon, is currently one of the most versatile pharmaceuticals for the treatment of human diseases in ophthalmology, neurology and dermatology

Botulinum toxin A, or Botox, has also become part of popular culture as a cosmetic enhancement tool for the ageing population

Although *Clostridium botulinum* and its toxins have been studied for hundreds of years, research continues to this day to understand its mechanisms of action and to find more applications in medicine

'prussic acid' and further studies ensued.<sup>9</sup> In 1871, the term 'botulus', from the Latin word for 'sausage', was given to this disease.<sup>10</sup> Even in the early 1900s, botulism outbreaks frequently occurred in the USA.<sup>3</sup> Because of these problems, Dole Food Company, Inc. developed novel food canning technologies during the 1920s, which have made this company today one of the world's largest distributors of canned foods. Symptoms of botulism include disturbances in vision, speech and swallowing.<sup>3</sup> Asphyxia and death commonly occur 18–36 hours after the ingestion of the toxin. Without treatment, the mortality rate ranges from 10 to 65%.

### Dr Justinus Kerner (1786–1862)

Justinus Kerner was a German physician and poet. He was also known as Würst (German term for 'sausage') Kerner because of his work with the mysterious 'sausage poison'. In 1817 and 1820, he published the first case studies on botulinum intoxication, and in 1822 he wrote the first complete monograph on the 'fatty toxin' from sour sausages.<sup>9</sup> Based on heroic experiments conducted upon himself and laboratory animals, Kerner made several important observations about the toxin:

- It develops in sour sausages under anaerobic conditions
- It interrupts motor signal transmission in the peripheral and autonomic system
- It is lethal in small doses.

Kerner also accurately described all the neurological symptoms of botulism recognised in modern medicine including vomiting, intestinal spasms, mydriasis, ptosis, dysphagia and respiratory failure.<sup>9,11</sup> Furthermore, he proposed that the toxin be used for therapeutic purposes such as lowering sympathetic nervous system activity associated with movement disorders (ie 'Veitstanz' or chorea minor) and hypersecretion of body fluids (ie sweat, mucus), ulcers from malignant diseases, delusions, rabies, plaque, and consumption from lung tuberculosis and yellow fever.<sup>12</sup> Although many attempts at artificially reproducing the toxin failed, Kerner postulated that the poison was of zoonic (biologic, animal) origin, a bold statement at a time in history where microscopic pathogens had not yet been discovered.

### Dr Emile Pierre van Ermengem (1851–1922)

Emile van Ermengem was a microbiologist and trained in Berlin under Robert Koch (1843–1910) who was the first researcher to prove that certain microorganisms could cause disease in animals. Koch's most noted discoveries included anthrax (1880), tuberculosis (1882), and cholera (1883). In 1895, a botulism outbreak occurred after a funeral in the Belgian village of Elezelles, and van Ermengem was the first to correlate botulism with a bacterium found in raw, salted pork and the postmortem tissue of victims who had consumed the contaminated meat.<sup>13,14</sup> After van Ermengem had successfully isolated this bacterium, he named it *Bacillus botulinus*,<sup>14</sup> which was renamed *Clostridium botulinum* in later years.

## Botulinum toxin and biological warfare

The first attempts to develop biological and chemical weapons began in Germany during World War I. None were successful. With the onset of World War II, the American government began intensively researching biological weapons. The United States Office of Strategic Services devised a plan to use Chinese prostitutes to assassinate high-ranking Japanese officers by concealing a lethal dose of botulinum toxin in a pin-size gelatin capsule to be slipped into food or drink. A large batch of capsules was prepared and sent to the US Navy detachment in Chunking, China, for testing. The capsules were used on stray donkeys and, because the animals survived, the project was abandoned.<sup>15</sup> The debate about whether donkeys are immune to botulism continues.

The ideal biological weapons are easily concealed, and cause transmissible disease and high mortality rates, creating panic and disruption in society.<sup>16</sup> It was once thought that botulinum toxin was an ideal weapon because it had many of these properties. Today, botulinum toxin is still considered the most poisonous substance in the world: one gram has the potential to kill one million people. Nevertheless, botulinum toxin is actually a poor choice as a biological weapon because:

- it must be ingested in sufficient quantities
- mortality rates with ingestion are variable
- it is rapidly inactivated by standard water sanitation protocols
- it is not transmissible from one person to another
- botulism can be effectively treated with botulinum antitoxin, ciprofloxacin or other broad-spectrum antibiotics.<sup>16</sup>

Furthermore, modern biological warfare has developed much more effective weapons, including anthrax, smallpox, plague and viral infections.

### Fort Detrick – a research facility for biological weapons and botulinum toxin

During World War II, the US Academy of Sciences created a laboratory named Fort Detrick in Maryland for the investigation of dangerous infectious bacteria and toxins that could be used in war. The facility was established by Professors EB Fred and Ira Baldwin from the University of Wisconsin and Stanhope Bayne-Jones from Yale University. Many other bacteriologists and physicians were also stationed at Fort Detrick for this purpose.<sup>4</sup> Many years earlier, in the 1920s, Dr Herman Sommer and colleagues at the University of California had obtained a crude botulinum toxin type A concentrate from culture fluid by acidic preparation.<sup>17</sup> In 1946, researchers at Fort Detrick obtained a crystalline form of botulinum toxin A and the method was subsequently used by Dr Edward Schantz to produce the first batch of botulinum toxin for use in humans.<sup>4,18</sup>

In 1972, President Nixon signed the Biological and Toxin Weapons Convention, which terminated all research on biological agents for use in war. Fort Detrick was formally closed in that year, but research into the use of botulinum and other food-

borne toxins for medicinal use continued at the University of Wisconsin under the leadership of Edward Schantz.<sup>4</sup> By 1979, Schantz had produced a sufficiently large batch of botulinum toxin A, named batch 79–11, consisting of 200 mg of twice crystallised toxin approved by the FDA for use in humans. This original preparation maintained its toxicity and was in use until December 1997.<sup>18</sup> Between 1980 and 1990, a Master Batch Record was written for the manufacture of medical grade botulinum toxin, and in 1991 several batches of botulinum toxin A as well as research findings were bought by a pharmaceutical company named Allergan Inc. The agent was subsequently given the name Botox.<sup>4</sup>

## Current uses of botulinum toxin for human disease

### Ophthalmology

Botulinum was first used to treat human disease over 25 years ago by Drs Alan Scott and Edward Schantz in 1968. In the 1960s, Scott, an ophthalmologist at the Smith-Kettlewell Eye Research Institute in San Francisco, began researching substances to inject into the hyperactive muscles involved with strabismus as an alternative to conventional surgery. His intention was to find a substance that could block neurotransmission and reduce muscle activity. Although several substances were tried in monkeys with surgically induced strabismus, Scott did not find success until he approached Schantz about the botulinum toxin.<sup>19</sup> In 1978, Scott was given FDA permission to inject botulinum toxin into human volunteers for strabismus.<sup>18</sup> Today, indications for botulinum toxin A use in ophthalmology include blepharospasm, strabismus, and other conditions of hyperactive extraocular muscles. Doses are typically less than 30 U.<sup>4</sup>

### Neurology

While ophthalmologists all around the world began injecting botulinum toxin into tiny eye muscles for strabismus, other specialists and surgeons began their own investigations into the use of botulinum toxin in humans. Neurologists recognised that botulinum toxin injections would be effective for neurochemical blockade of involuntary muscle contraction in larger muscle groups. By the 1980s, the toxin was used to correct tremors and spasms of the face, eyelid, trunk and limbs. In 1989, the FDA approved botulinum toxin A for the treatment of involuntary muscle contractions, strabismus, blepharospasm and hemifacial spasm. Today, botulinum toxins A and B are also used off-label in neurology to treat torticollis, almost all forms of dystonias, spasticity, tremors, vocal disorders, cerebral palsy in children, gastrointestinal disorders, tension and migraine headaches, and pain syndromes.<sup>2,8,20,21</sup> Doses up to 300 U may be used, depending on the size of the muscle groups and treatment area.<sup>4</sup>

### Dermatology

Since the 1990s, Botox has become well known by the public as a means of cosmetic enhancement. The story of its use in der-

matology is familiar to many Canadians. In 1987, ophthalmologist Jean Carruthers observed that frown lines disappeared after the use of botulinum toxin A for blepharospasm. Dr Carruthers shared her observations with her husband, Alastair Carruthers, a dermatologist. Together, the Carruthers had stumbled upon a cosmetic procedure that revolutionised the field of cosmetic enhancement procedures.

Since 1992, the Canadian couple has promoted the use of Botox via educational and training campaigns. In 1996, they published the first paper on the use of Botox for cosmetic purposes,<sup>22</sup> and another group from Columbia University noted similar applications, although their findings were not published until later.<sup>23</sup> Today, botulinum toxin is used in dermatology for the treatment of vertical glabellar frown and horizontal forehead lines, wrinkles from actinic damage, lateral canthal lines (crow's feet), nasal flare, eyebrow elevation or shaping, facial asymmetry, upper lip creases and chin dimpling. Reports since the mid-1990s have also described Botox as highly effective for hyperhidrosis of the axilla, palms of the hands and soles of the feet,<sup>24</sup> and a useful adjunctive medication with laser resurfacing and other cosmetic procedures.<sup>25</sup> Doses range from 3 U for small muscles of the face and up to 300 U for larger treatment areas, such as those of hyperhidrosis.<sup>26</sup>

## Conclusion

Botulinum toxin A injections are performed millions of times a year around the world. Once a food poison and later exploited as a biological weapon, botulinum toxin is currently one of the most versatile pharmaceuticals for the treatment of human diseases in ophthalmology, neurology and dermatology. Botulinum toxin A has also become integrated into popular culture as a cosmetic enhancement tool for the ageing population. Although *Clostridium botulinum* and its toxins have been studied for hundreds of years, research into its mechanisms of action and further medical applications continues to this day.

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