

Botulinum Toxin: Lethal Weapon or Magic Bullet?

Timeline

Note: Dates of particular significance for scientific advances are indicated in **bold**.

- 800s Emperor Leo VI of Byzantine forbids sausage manufacturing.
- 1793 Wildbad, Germany experiences a large outbreak of food poisoning due to consumption of contaminated blood sausages.
- 1795-1813 Hygienic standards of rural food production in Stuttgart, Germany are on decline due to economic constraints resulting from the Napoleonic warfare.
- 1802 The Stuttgart government issues a public notice about the harmful effects of smoked blood sausage consumption.
- 1817-1822 German physician and poet Justinius Kerner identifies over 155 cases of food poisoning. Muller, another German physician, later describes the collective symptoms of these patients as Kerner's Disease.
- 1822 Kerner identifies a fatty acid substance that he calls "sausage poison" and suggests methods of treatment and prevention of the food poisoning. He also publishes ideas for therapeutic use of the toxic fatty acid to treat diseases associated with an overactive nervous system.
- 1895 Professor Emile Pierre van Ermengem, of Ellezelles, Belgium identifies the bacterium *Bacillus botulinus* as the causative agent for botulism poisoning. During an outbreak of contaminated preserved ham, he uses Koch's postulates to determine the cause of disease.**
- 1928 Dr. Herman Sommer at UCSF isolates botulinum neurotoxin in purified form as a stable acid precipitate.**
- 1943 WWII foreign intelligence reports indicate that many countries are engaged in biowarfare programs. In response, the U.S. National Academy of Sciences and Fred Ira Baldwin, chairman of the bacteriology department of the University of Wisconsin, decide to set up laboratories at Camp Detrick, Maryland for offensive and defensive biowarfare research.
- 1946 Dr. Edward Schantz, a young U.S. army officer stationed at Fort Detrick, with other colleagues, purifies botulinum neurotoxin in great quantities for use in government and educational institutions. The US Office of Strategic Services (OSS) develops a plan for Chinese prostitutes to assassinate high-ranking Japanese officers using small gelatin capsules containing a lethal dose of botulinum toxin.

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- 1949** A.S.V. Burgen discovers that botulinum toxin blocks neurotransmitter release at the neuromuscular junction.
- 1950s** Dr. Vernon Brooks discovers that botulinum toxin type A (BoNT/A), when injected into a hyperactive muscle, blocks the release of acetylcholine from motor nerve endings.
- 1969 The U.S. forswears the use of biological weapons and declares that it will unilaterally destroy all their biological weapons stocks.
- 1972 The Biological and Toxins Weapons Convention Treaty is signed by over 100 countries and President Nixon orders Fort Detrick to close its laboratories for biological agents offensive programs. Schantz goes to the University of Wisconsin to continue his research.
- 1960s** Dr. Schantz and Dr. Alan B. Scott, M.D., of the Smith-Kettlewell Eye Research Foundation, test botulinum toxin type A in monkeys to determine if it is an effective therapy for strabismus (crossed eyes).
- 1970 Dr. Scott forms his own company called Oculinum to develop botulinum neurotoxin as a therapeutic for strabismus.
- 1978 Dr. Scott receives permission from the Food and Drug Administration (FDA) to test botulinum toxin type A in human volunteers. Original batch is 150 mg and is used for more than 250,000 injections in humans. For many years, this was the only batch approved by the FDA, which requires batch approval for biological drugs.
- 1982** A multicenter clinical trial to test botulinum neurotoxin for the treatment of strabismus is organized and tests over 7,000 patients. The toxin is used by many dermatologists and physicians before it is approved by the FDA for licensing.
- 1987 Dr. Alastair Curruthers, a Canadian dermatologist, uses botulinum toxin type A in an off-label indication to remove wrinkles from his receptionist's forehead (Cathy Bickerton Swann).
- 1988 Allergan acquires rights to use botulinum neurotoxin from Oculinum and began to conduct clinical trials for other toxin indications, including cervical dystonia.
- 1989 Oculinum, Inc. receives FDA approval to market botulinum toxin type A in the United States as an orphan drug to treat strabismus, blepharospasm, and hemifacial spasm associated with dystonia in patients 12 years of age and older.

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- 1990** Heiner Niemann, of the Federal Research Center for Viruses and Diseases a of Animals, Tübingen, Germany, determines the DNA sequence of botulinum toxin. It is found to have homology with zinc dependent proteases.
- 1991 Allergan buys the Oculinum company and changes the product's name to BOTOX.
- 1992** Synaptobrevin/VAMP, a protein involved in synaptic vesicle movement, is identified as a molecular target of BoNT/B.
- 1993** Synaptobrevin, syntaxin and SNAP-25 are identified as proteins essential for synaptic vesicle transmission. Synaptobrevin is found to reside on the vesicle, while syntaxin and SNAP-25 reside on the plasma membrane. That same year, syntaxin and SNAP-25 are identified as molecular targets of BoNT/C and BoNT/A, respectively.
- 1997 The FDA approves a new bulk toxin source for use in the manufacture of BoNT/A. The new product, called *current* BOTOX, is comparable in clinical efficacy to the *original* BOTOX, but the higher specific potency reduces the amount of neurotoxin protein utilized, which in turn, leads to a reduction in the production of antibodies
- 2000 The FDA approves BOTOX (Botulinum toxin type A) manufactured by Allergan for the treatment of abnormal head position and neck pain associated with cervical dystonia. The FDA also approves Myobloc-TM for the same indication. Myobloc is the U.S. trade name for botulinum toxin type B from Elan Pharmaceuticals (Neurobloc in Europe).
- 2001 The UK approves BOTOX (BoNT/A) synthesized by Allergan for axillary hyperhidrosis (excessive sweating). Canada approves Botox (BoNT/A) synthesized by Allergan for axillary hyperhidrosis (excessive sweating), focal muscle spasticity, and for cosmetic treatment of wrinkles at the browline.
- 2001 President Bush declines to ratify the Biological and Toxins Weapons Convention Treaty, arguing that the inspections protocol would jeopardize commercial biotechnology industries in the U.S.
- 2002 The FDA approves BOTOX (BoNT/A) synthesized by Allergan for cosmetic treatment of wrinkles at the brow line. Clinical trials with BOTOX, Dysport and Myobloc are underway for other indications such as cerebral palsy, migraine and chronic back pain.