

History of Botulinum Toxin Therapy

Iara Debert, MD, PhD & Joel M Miller, PhD
Eidactics, San Francisco

From Sausage Poisoning To Therapy

In 1820, Justinus Kerner, a small-town German medical officer and romantic poet, gave the first complete description of clinical botulism based on extensive clinical observations of so-called “sausage poisoning” (Kerner 1820). Following experiments on animals and on himself, he concluded that the toxin acts by interrupting signal transmission in the somatic and autonomic motor systems, without affecting sensory signals or mental functions. He observed that the toxin develops under anaerobic conditions, and can be lethal in minute doses (Kerner 1822). His prescience in suggesting that the toxin might be used therapeutically to block both abnormal movements and hypersecretions earned him recognition as the intellectual founder of modern botulinum toxin therapy (Erbguth & Naumann 1999).

Seventy-five years later, Émile van Ermengem, professor of bacteriology and a student of Robert Koch, correctly described *Clostridium botulinum* as the bacterial source of the toxin. Thirty-four attendees at a funeral were poisoned by eating partially salted ham, an extract of which was found to cause botulism-like paralysis in laboratory animals. Van Ermengem (1897) isolated and grew the bacterium, and described its toxin, which was later purified by P Tessmer Snipe and Hermann Sommer (1928).

Over the next three decades, as food canning was approaching a billion dollar a year industry, botulism was becoming a public health hazard. Karl Friedrich Meyer, a prodigiously productive Swiss-American veterinary scientist (and supervisor of Alan B Scott’s mother’s 1925 MA degree in bacteriology!), created a center at the Hooper Foundation in San Francisco, where he developed techniques for growing the organism and extracting the toxin, and conversely, for preventing organism growth and toxin production, and inactivating the toxin by heating. The California canning industry was thereby preserved.

With the outbreak of World War II, weaponization of botulinum toxin was investigated at Fort Detrick in Maryland. Carl Lamanna and James Duff (1946) developed the concentration and crystallization techniques that Edward J Schantz used to create the first clinical product. When the Army’s Chemical Corps was disbanded, Schantz moved to the Food Research Institute in Wisconsin, where he manufactured toxin for experimental use and generously provided it to the academic community.

The mechanism of botulinum toxin action – blocking the release from nerve endings of the neurotransmitter acetylcholine – was elucidated in the mid-1900s (Burgen et al 1949), and remains an important research topic. Nearly all toxin treatments are based on this effect in various body tissues.

A Treatment for Eye Muscle Disorders

Ophthalmologists specializing in eye muscle disorders (*strabismus*) had developed the method of *EMG-guided injection* (using the *electromyogram*, the electrical signal from an activated muscle, to guide injection) of local anesthetics as a diagnostic technique for evaluating an individual muscle's contribution to an eye movement (Magoon et al 1982). Because strabismus surgery frequently needed repeating, a search was undertaken for non-surgical, injection treatments using various anesthetics, alcohols, enzymes, enzyme blockers, and snake neurotoxins. Finally, inspired by Daniel Drachman's work (1964) with chicks at Johns Hopkins, Alan B Scott and colleagues injected botulinum toxin into monkey extraocular muscles (1973). The result was remarkable: a few picograms induced paralysis that was confined to the target muscle, long in duration, and without side-effects.

After working out techniques for freeze-drying, buffering with albumin, and assuring sterility, potency, and safety, Scott was granted FDA approval for investigational use, and began manufacturing botulinum type A neurotoxin in his San Francisco lab. He injected the first strabismus patients in 1977, reported its clinical utility in 1980 (Scott), and had soon trained hundreds of ophthalmologists in EMG-guided injection of the drug he named *Oculinum*[™] ("eye aligner").

Strabismus is caused by imbalances in the actions of muscles that rotate the eyes, and can sometimes be relieved by weakening a muscle that pulls too strongly, or pulls against one that has been weakened by disease or trauma. Muscles weakened by toxin injection recover from paralysis after several months, so it might seem that injection would then need to be repeated. However, muscles adapt to the lengths at which they are chronically held (Scott 1994), so that if a paralyzed muscle is stretched by its antagonist, it grows longer, while the antagonist shortens, yielding a permanent effect. If there is good binocular vision, the brain mechanism of *motor fusion*, which aligns the eyes on a target visible to both, can stabilize the corrected alignment.

Treatment of Other Muscle Disorders

By 1982, eye muscles had been injected for strabismus and *nystagmus* (jerky, involuntary eye movements), eyelid muscles for retraction and *blepharospasm* (sustained, involuntary contractions of muscles around the eye), facial muscles for hemifacial spasm, and limb muscles for *dystonia* (sustained muscle spasm), all as predicted in Scott's 1973 study.

Scott also injected the first cases of *torticollis* (painful, spastic twisting of the neck), which were later published by Joseph Tsui of Vancouver (1985). But even a century and a half after Kerner's work, it was difficult for many to accept that the specificity and molecular tenacity that made ingested toxin so deadly also made it safe when injected directly into a target muscle, and no Bay Area neurology, orthopedic, or rehabilitation physician would try toxin for muscle contractures with stroke, dystonia, torticollis, or cerebral palsy. L Andrew Koman (1993) of Wake Forest University in North Carolina pioneered use of toxin to treat pediatric leg spasm in cerebral palsy.

Patient groups quickly spread the word that there were now effective treatments for previously untreatable motility disorders such as blepharospasm, which can result in functional blindness despite an otherwise normal visual system. Torticollis patients discovered that their pain could be markedly reduced by toxin injection, motility increased, head position somewhat improved, even if tremor was not. Pankaj Pasricha (1993) showed that botulinum toxin could be used for the treatment of *achalasia*, a spasm of the lower esophageal sphincter. *Spasmodic dysphonia* (a speaking difficulty), various gastroenteric and urinary sphincter spasms, muscle spasm in stroke, and many other muscle disorders, were also treated with botulinum toxin injection.

In January 2014, botulinum toxin was approved by UK's Medicines and Healthcare Products Regulatory Agency (MHRA) for treatment of restricted ankle motion due to lower limb spasticity associated with stroke in adults.

Botulinum toxin has not been approved for pediatric use, although it has been used off-label for several pediatric conditions, including infantile esotropia (Scott et al 1990; De Alba Campomanes et al 2010) and spastic conditions in cerebral palsy (Ryll et al 2011; Pin et al 2013).

Supply & Demand

In 1986, Oculinum Inc, Scott's micromanufacturer and distributor of botulinum toxin, was unable to obtain product liability insurance, and could no longer supply the drug. As supplies became exhausted, patients who had come to rely on periodic injections became desperate. For 4 months, pending resolution of liability issues, American blepharospasm patients traveled to Canadian eye centers for their injections (Boffey 1986).

Based on data from thousands of patients collected by 240 investigators, under the 1983 US Orphan Drug Act, Scott got FDA approval in 1989 to market Oculinum for clinical use in the United States to treat adult strabismus and blepharospasm. Allergan served as the drug's distributor for almost 2 years, and in 1991 took over the licenses and changed the drug's name to *Botox*®.

Treatment of Hypersecretion

Finally pursuing Kerner's suggestion 175 years earlier, Khalafalla Bushara and David Park (1994) made the first non-muscular use of botulinum toxin in humans with a demonstration that injections could inhibit excess sweating.

The toxin was also used to treat hyperhidrosis (Drobik & Laskawi 1995) in Frey's Syndrome, in which facial sweating occurs after parotid gland surgery due to anomalous regrowth of injured salivary nerves to the face. It was a natural extension to use the toxin to ameliorate the poorly handled salivary secretions in amyotrophic lateral sclerosis and to decrease excessive lacrimal gland secretion. The concept of blocking cholinergic innervation to sweat glands as a treatment for hyperhidrosis in the axilla, hands, and elsewhere, followed.

Cosmesis

Richard Clark, a plastic surgeon from Sacramento (CA), was the first to document a cosmetic use for botulinum toxin. He treated facial asymmetry caused by unilateral facial nerve paralysis by injecting toxin into the non-paralyzed frontal muscle (Clark & Berris 1989).

Marrying ophthalmology to dermatology, Jean and Alistair Carruthers (1992) observed that blepharospasm patients who received injections around the eyes and upper face also enjoyed diminished facial *glabellar* lines (“frown lines” between the eyebrows), thereby initiating the highly-popular cosmetic use of the toxin. Monte Keen (1994) at Columbia University made similar reports. In 2002, following clinical trials, the FDA approved *Botox Cosmetic*, botulinum A toxin to temporarily improve the appearance of moderate-to-severe glabellar lines.

Treatment of Chronic Pain

William Binder (2000) reported that patients who had cosmetic injections around the face reported relief from chronic headache. This was initially thought to be an indirect effect of reduced muscle tension, but it is now known that the toxin inhibits release of peripheral nociceptive neurotransmitters, suppressing the central pain processing systems responsible for migraine headache (Jackson et al 2012; Ramachandran & Yaksh 2014). In 2010, the FDA approved intramuscular botulinum toxin injections for prophylactic treatment of chronic migraine headache.

Bibliography

- Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pogoda JM (2000). Botulinum toxin type a (botox) for treatment of migraine headaches: An open-label study. *Otolaryngol Head Neck Surg*, vol 123, isu 6, pgs 669-676.
- Boffey P (1986) Loss of drug delegates many to blindness again. *The New York Times*.
- Burgen AS, Dickens F, Zatman LJ (1949). The action of botulinum toxin on the neuro-muscular junction. *J Physiol*, vol 109, isu 1-2, pgs 10-24.
- Bushara KO, Park DM (1994). Botulinum toxin and sweating. *J Neurol Neurosurg Psychiatry*, vol 57, isu 11, pgs 1437-1438.
- Carruthers JD, Carruthers JA (1992). Treatment of glabellar frown lines with c. Botulinum-a exotoxin. *J Dermatol Surg Oncol*, vol 18, isu 1, pgs 17-21.
- Clark RP, Berris CE (1989). Botulinum toxin: A treatment for facial asymmetry caused by facial nerve paralysis. *Plast Reconstr Surg*, vol 84, isu 2, pgs 353-355.
- De Alba Campomanes AG, Binenbaum G, Campomanes Eguiarte G (2010). Comparison of botulinum toxin with surgery as primary treatment for infantile esotropia. *J AAPOS*, vol 14, isu 2, pgs 111-116.
- Drachman DB (1964). Atrophy of skeletal muscle in chick embryos treated with botulinum toxin. *Science*, vol 145, isu 3633, pgs 719-721.
- Drobik C, Laskawi R (1995). Frey's syndrome: Treatment with botulinum toxin. *Acta Otolaryngol*, vol 115, isu 3, pgs 459-461.
- Erbguth FJ, Naumann M (1999). Historical aspects of botulinum toxin: Justinus kerner (1786-1862) and the "sausage poison". *Neurology*, vol 53, isu 8, pgs 1850-1853.
- Ermengem EV (1897). Ueber einen neuen anaëroben bacillus und seine beziehungen zum botulismus". *Zeitschrift für hygiene und infektionskrankheiten*, vol 26, isu 1, pgs 1-56.
- Jackson JL, Kuriyama A, Hayashino Y (2012). Botulinum toxin a for prophylactic treatment of migraine and tension headaches in adults: A meta-analysis. *JAMA*, vol 307, isu 16, pgs 1736-1745.
- Keen M, Kopelman JE, Aviv JE, Binder W, Brin M, Blitzer A (1994). Botulinum toxin a: A novel method to remove periorbital wrinkles. *Facial Plast Surg*, vol 10, isu 2, pgs 141-146.
- Kerner J (1820). Neue beobachtungen über die in württemberg so häufig vorkommenden tödlichen vergiftungen durch den genuss geräucherter würste. Tübingen: Osiander.
- Kerner J (1822). Das fettgift oder die fettsäure und ihre wirkungen auf den thierischen organismus, ein beytrag zur untersuchung des in verdorbenen würsten giftig wirkenden stoffes. Stuttgart, tübingen: Cotta.

- Koman LA, Mooney JF, 3rd, Smith B, Goodman A, Mulvaney T (1993). Management of cerebral palsy with botulinum-a toxin: Preliminary investigation. *J Pediatr Orthop*, vol 13, isu 4, pgs 489-495.
- Lamanna C, Mc EO, Eklund HW (1946). The purification and crystallization of clostridium botulinum type a toxin. *Science*, vol 103, isu 2681, pgs 613.
- Magoon E, Cruciger M, Scott AB, Jampolsky A (1982). Diagnostic injection of xylocaine into extraocular muscles. *Ophthalmology*, vol 89, isu 5, pgs 489-491.
- Pasricha PJ, Ravich WJ, Kalloo AN (1993). Botulinum toxin for achalasia. *Lancet*, vol 341, isu 8839, pgs 244-245.
- Pin TW, Elmasry J, Lewis J (2013). Efficacy of botulinum toxin a in children with cerebral palsy in gross motor function classification system levels iv and v: A systematic review. *Dev Med Child Neurol*, vol 55, isu 4, pgs 304-313.
- Ramachandran R, Yaksh TL (2014). Therapeutic use of botulinum toxin in migraine: Mechanisms of action. *Br J Pharmacol*, vol 171, isu 18, pgs 4177-4192.
- Ryll U, Bastiaenen C, De Bie R, Staal B (2011). Effects of leg muscle botulinum toxin a injections on walking in children with spasticity-related cerebral palsy: A systematic review. *Dev Med Child Neurol*, vol 53, isu 3, pgs 210-216.
- Scott AB (1980). Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology*, vol 87, isu 10, pgs 1044-1049.
- Scott AB (1994). Change of eye muscle sarcomeres according to eye position. *J Pediatr Ophthalmol Strabismus*, vol 31, isu 2, pgs 85-88.
- Scott AB, Rosenbaum A, Collins CC (1973). Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol*, vol 12, isu 12, pgs 924-927.
- Scott AB, Magoon EH, Mcneer KW, Stager DR (1990). Botulinum treatment of childhood strabismus. *Ophthalmology*, vol 97, isu 11, pgs 1434-1438.
- Snipe Pt SH (1928). Studies on botulinus toxin 3. Acid precipitation of botulinus toxin. *Journal of Infectious Diseases*, vol 43, isu 2, pgs 152-160.
- Tsui JK, Eisen A, Mak E, Carruthers J, Scott A, Calne DB (1985). A pilot study on the use of botulinum toxin in spasmodic torticollis. *Can J Neurol Sci*, vol 12, isu 4, pgs 314-316.