

Blood Sausage to BOTOX: The Story of the Miracle Toxin

Introduction

Many of the scientific discoveries in medical history have shown how human endeavor can turn a bane into a boon. The journey of botulinum toxin from a lethal poison to a legally approved medicine is fascinating. From the tragedy of blood sausage to the strategic use in strabismus, from hyperactive extraocular muscular disorder to hyperhidrosis, the realm of therapeutic potentials of botulinum toxin is still expanding.

Ancient period to pre-Kerner era

The history of botulinum toxin goes back to antiquity. In ancient India, kings probably used it to slay their enemy counterparts. In a dietary edict of the tenth century, Emperor Leo VI of Byzantium forbade the manufacture of blood sausage which might have originated from the incidences of food poisoning.^[1] The earliest historical records date back to 1735 and 1793 when several people succumbed after taking blood sausage.^[2] In July 1802, the Royal Government in Stuttgart, and in August 1811, the medical section of the Department of Internal Affairs of the Kingdom of Württemberg pronounced caution against “sausage poisoning” and presumed it to be caused by hydrocyanic acid then known as *prussic acid*.^[3]

Lethal sausage to genius Kerner

In 1793, out of 13 people afflicted with sausage poisoning in Wildbad of West Germany, six died. Justinus Andreas Christian Kerner, a German poet and a physician [Figure 1] working in Wildbad published the first case studies on sausage poisoning in 1817 as “*Tübinger Blätter für Naturwissenschaften und Arzneykunde*” and suspected a “fat poison” to be the offender of this disaster. This “fat poison”

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was later identified as botulinum toxin. Kerner published his further studies involving 76 patients in a monograph entitled “*Neue Beobachtungen über die in Württemberg so häufig vorkommenden tödtlichen Vergiftungen durch den Genuß geräu-cherter Würste*” (1820) [Figure 2], and again in 1822, he published his second monograph “*Das Fettgift oder die Fettsäure und ihre Wirkungen auf den thierischen Organismus, ein Beytrag zur Untersuchung des in verdorbenen Würsten giftig wirkenden Stoffes*” comprising case reports of 155 subjects. He not only gave an accurate and vivid description of botulinum poisoning, but also performed experiments to observe the effect of the toxin on various animals including himself. John Müller in 1869 coined the term *botulism* from the Latin word *botulus* meaning sausage.^[3,4]

Bacillus to BOTOX

The Belgian microbiologist Emile Pierre Marie van Ermengem of the University of Ghent identified *Bacillus botulinus* (later known as *Clostridium botulinum*) in 1895–97.^[3] Though Kerner, with his astute observation and clinical intuition, predicted in the eighth chapter of the second monograph (1822) about the clinical use of the poison in minute amounts, Alan B Scott pioneered the therapeutic use of botulinum toxin in the 1980s.^[5] In the 1990s, Carruthers *et al.* used it in the management of glabellar lines, and this revolutionized the world of cosmetic enhancement procedures.^[6] The enormous potential of this drug led to its application in various branches of medicine in general and dermatology and esthetic medicine in particular [Table 1].

The other botulinum toxins

In 1904, an outbreak of botulinum toxin poisoning happened from canned beans in

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Figure 1: Justinus Andreas Christian Kerner (1786-1862). (Credit: Ottavio d'Albuzzi († 1855), Public domain, via Wikimedia. Source: Commons https://commons.wikimedia.org/wiki/File:Justinus_Kerner_1852_von_Ottavio_d%27Albuzzi.jpg)

Darmstadt, Germany. This led to the change of notion that botulism only can happen from meat or fish. Landmann isolated the bacterium, and Leuchs examined and compared it with the already-known one, only to find that the two are different strains. Later Georgina Burke designated them botulinum toxin types A and B, respectively. Afterward, Bengston in the United States and Seddon from Austria described type C in 1922. This was followed by types D (Meyer and Gunnison, 1928), type E (Bier, 1936), type F (Moller and Scheibel, 1960), and type G (Gimenex and Ciccarelli, 1970). Out of these variants, type A got its approval in the United Kingdom (UK) and United States (US) for therapeutic use in dermatology in 2001 and 2002 respectively and serotypes C, E, and F are under evaluation for their therapeutic potential.^[1]

Epilogue

The chequered history of botulinum toxin in the world of medicine is fascinating. The lethal toxin has turned into an important weapon in the therapeutic armamentarium in ophthalmology, neurology, dermatology, esthetic medicine, and several other branches of medical science. Kerner

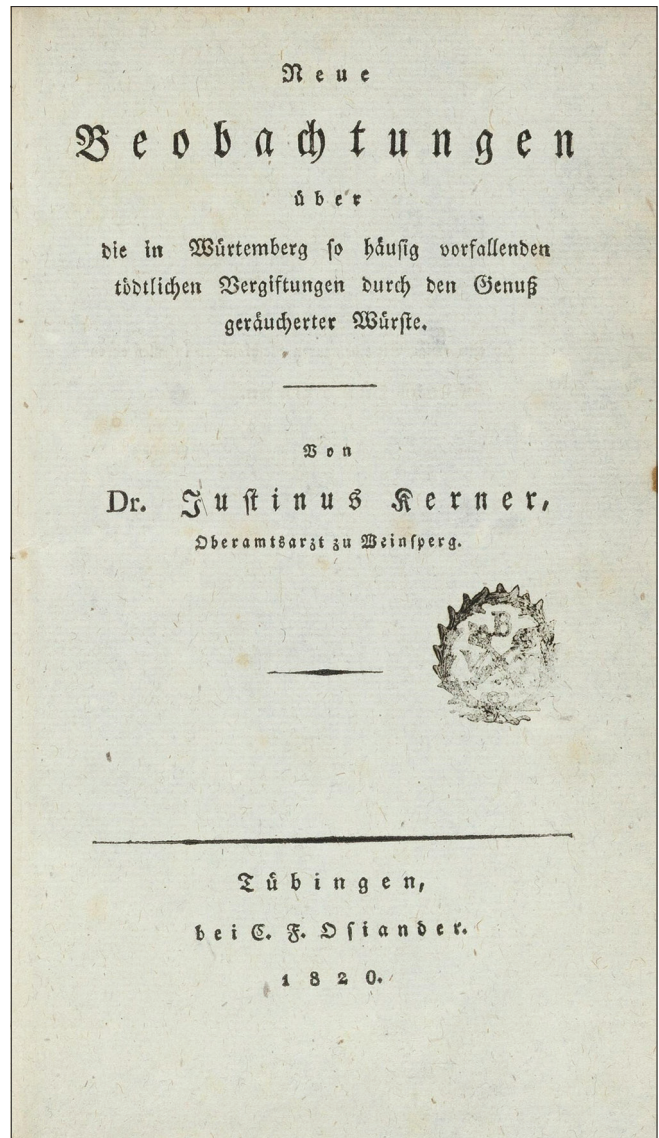


Figure 2: Title page of "Neue Beobachtungen über die in Württemberg so häufig vorkommenden tödtlichen Vergiftungen durch den Genuß geräucherter Würste" (1820). (Courtesy of: Eberhard Karls Universität Tübingen. Source: <http://idb.ub.uni-tuebingen.de/diglit/J1136a>. Public domain)

will be remembered in the medical world not only for his invaluable contribution regarding the detection of the cause of a deadly disease, but also for his hypothesis about the potential therapeutic use of "toxic fat poison" that led to the research which turned a fatal poison into a miracle toxin.

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Conflicts of interest

There are no conflicts of interest.

Table 1: Evolution of botulinum toxin: Timeline

Timeline (in AD)	Person/authority concerned	Events
886	Emperor Leo IV of Byzantium	Forbade the manufacturing of blood sausage suspecting the role of it in fatal illness.
1817	German physician and poet Justinus Kerner (1786–1862)	First published a case study of blood sausage poisoning in Wildbad, Germany
1820	Kerner	Published the first monograph on sausage poisoning involving 76 patients
1822	Kerner	Published his second monograph containing a study on 155 patients and the first hypothesized therapeutic use of botulinum toxin.
1870	Müller	Coined the term <i>botulism</i> (Latin <i>botulus</i> =sausage)
1895	Emile Van Ermengem	First isolated the bacterium and named it <i>Bacillus botulinus</i> (it was later renamed <i>Clostridium botulinum</i>).
1919	Georgina Burke	Described botulinum toxin type B.
1922	Bengstone, Seddon	Described botulinum type C.
1928	Herman Sommer Meyer and Gunnison	First isolated in purified form and as a stable acid precipitate form known as botulinum toxin type A (BoNT-A). Described botulinum toxin type D.
1936	Bier	Described botulinum toxin type E.
1946	Edward J Schantz	Purified BoNT-A in crystalline form. Cultured <i>Clostridium botulinum</i> and isolated the toxin
1949	Arnold Burgen	Described neuromuscular transmission blocked
1950s	Vernon Brooks	Described the release of acetylcholine from motor nerve endings is blocked when BoNT-A is injected into a hyperactive muscle.
1960s	Edward Schantz and Alan B. Scott	Used BoNT-A in monkey experiments in blepharospasm
1960	Moller and Scheibel	Described botulinum toxin type F.
1970	Gimenex and Ciccarelli	Described botulinum toxin type G.
1980	Alan B. Scott	BoNT-A is used for the first time in humans to treat strabismus.
1989		The US FDA approves, Allergan's Oculinum (later BOTOX, on a botulinum toxin A) for the treatment of strabismus, blepharospasm, and hemifacial spas
1990	Carruthers <i>et al.</i>	Described the use of botulinum toxin in enhancing glabellar lines
2001		The United Kingdom approved BOTOX®, synthesized by Allergan, for axillary hyperhidrosis.
April 15, 2002		The US FDA announced the approval of BOTOX® to temporarily improve the appearance of moderate-to-severe glabellar lines.
September 11, 2013		The US FDA approved BOTOX® for the temporary improvement in the appearance of moderate to severe lateral canthal lines (crow's feet).
February 1, 2019		The US FDA approved Jeuveau® (prabotulinumtoxin A) for the temporary improvement of moderate-to-severe glabellar lines in association with corrugator and/or procerus muscle activity in adults.

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