

History of Botulinum Toxin

Kreyden OP, Böni R, Burg G (eds): Hyperhidrosis and Botulinum Toxin in Dermatology. Curr Probl Dermatol. Basel, Karger, 2002, vol 30, pp 77-93

.....

The History of Botulism

Michael L. Geiges

Department of Dermatology, University Hospital of Zurich, Switzerland

The History of Botulism

General Definition

Botulism is a form of food poisoning caused by the neurotoxin-producing bacterium *Clostridium botulinum*. The toxin inhibits the release of acetylcholine at the presynaptic nerve endings of the motor endplates, causing paralysis that begins with the cranial nerves and progresses caudally [1]. Although medical treatment has improved, the fatality rate in food-borne botulism is still between 5 and 10% [2]. Since the neurotoxin binds irreversibly to the presynaptic nerve endings, recovery from the effects of botulism takes many weeks and requires the growth of new nerve termini.

C. botulinum is an anaerobic gram-positive rod bacterium found ubiquitously in soil and damp environments. Subtypes A-G have been distinguished on the basis of the antigenic specificities of their respective toxins. Types A, B, E and very rarely F can cause food-borne botulism in humans. Types C and D are responsible for diseases in animals.

The neurotoxin, a protein, can be inactivated by heating at a temperature of 100 °C for 10 min. The spores of *C. botulinum*, however, are highly heat resistant; their inactivation requires humid heat at a temperature of more than 120 °C [1].

Different Types of Botulism

For about 150 years botulism has been thought to be caused exclusively by food that was contaminated with preformed toxins. This point of view changed in the 1970s, when botulism was found in babies who had ingested spores of *C. botulinum*: the spores germinated in the intestine and produced the toxin locally [3].

Five different types of botulism have been recognized in humans:

- (1) food-borne botulism, arising following ingestion of canned food contaminated with *C. botulinum* and preserved under anaerobic conditions;
- (2) infant botulism, where the toxin is produced locally in the intestine after the germination of ingested spores;
- (3) very rare cases in adults where no food source is identifiable, presumably an adult variant of infant botulism; the intestine is colonized by the bacteria;
- (4) wound botulism, with contamination and growth of *C. botulinum* in deep wounds under anaerobic conditions;
- (5) iatrogenic botulism as a side-effect of local therapy with botulinum toxin.

Clinical Appearance of Botulism

Clinical manifestations of botulism range from irritability to a disease that is fatal within 24 h! The first symptoms usually start 12–36 h after ingestion of the toxin. Typical symptoms are diplopia, double or blurred vision, bulbar weakness, dysphonia, dysarthria, dysphagia and dryness of the mouth. These symptoms are followed by a weakness in the muscles, which spreads downwards from the head to the neck, arms and thorax and finally to the legs, and can be accompanied by stomach pain, nausea and vomiting. Nausea and vomiting may also occur as early symptoms.

Further symptoms are constipation, urine retention, reduced tear flow and salivation, ptosis, difficulties in focussing the eyes and sometimes dilatation of the pupils. The patients remain conscious, are not disoriented or confused and have no sensory malfunctions. Depending on the dose, the symptoms occur either within hours or many days and can last for several weeks [1, 2].

Therapy and Prognosis of Botulism

Symptomatic therapy is the mainstay of therapeutic regimes for botulism. It includes artificial respiration, intubation and occasionally tracheotomy, a stomach or urine catheter etc., as necessary [1, 2].

An antitoxin is available, which, if given early enough, will improve the prognosis in cases of food-borne botulism [4]. In the other forms of botulism, the efficacy of antitoxin administration has not yet been established. Furthermore, if the antiserum is of equine origin, hypersensitivity reactions must be expected in 9–20% of cases [2, 5].

Antibiotics are indicated only when complications occur. Before the advent of intensive-care units, botulism was lethal in about 50% of cases. Today the mortality rate still lies around 5–10% in food-borne botulism and 2% in infantile botulism [1, 2].

First Descriptions of Botulism in the Medical Literature

Little is known about the history of the disease now defined as 'botulism' prior to the end of the 18th century. The definitions of infant botulism and wound botulism as independent entities are quite new and originated only in the last few decades. The history of 'classic' food-borne botulism closely parallels the history and development of food preservation techniques. Justinus Kerner (1786–1862), who published the first detailed monograph on so-called 'Fleischvergiftungen' (meat poisoning) in the 1820s, wrote that the edict prohibiting the manufacture of blood sausages, issued for religious reasons by Leo VI of Byzantium (emperor from 889 to 911), incidentally saved many lives [6]. However, it is a matter of speculation whether cases of poisoning with the toxin of *C. botulinum* could actually have already appeared at this epoch. Different concepts of disease led to different emphases in the documentation in the pre-scientific era of medicine. The first reliable sources relating botulism to disease are probably the accounts of the sausage poisonings in Württemberg that date from the end of the 18th century. All the more impressive is the accurate, detailed description of the symptoms and, in particular, of the course of disease as described in the first recorded account of botulism, published in 1817 in the *Tübinger Blätter* [7, 8].

The Work of Justinus Kerner

The First Clinical Descriptions of Food Poisoning Caused by Spoiled Sausages

In Württemberg towards the end of the 18th century, there were periodic reports of fatal illnesses following the consumption of sausages. Some authors suspect that the general shortage of food at that time and the poor hygienic conditions led to this apparent increase in the number of cases of food poisoning [9]. However, it is more likely that peculiarities in the way the Württemberg people made and, in particular, stored the sausages (in closed wooden boxes rather than on straw as was customary elsewhere) were responsible for this regional accumulation of poisonings [10].

In 1802, this 'sausage poisoning disease' came to the attention of the health authorities of the Württemberg government. The disease was not unknown to the physicians of that time – the symptoms were vomiting, diarrhoea, but also urine retention, double vision, difficulty in swallowing etc. The cause of the disease was suspected to be an organic poison, most probably prussic acid, that originated in the spoiled sausages [11].

Finally Johann Heinrich Ferdinand Autenrieth (1772–1835), professor of medicine at the University of Tübingen, began to collect and work on cases of

sausage poisoning. In 1817, he published the observations of Georg Steinbuch (1770–1818) and Justinus Kerner under the title 'Medizinische Polizey' in the *Tübinger Blätter* [7, 8, 11]. [The term 'medizinische Polizey', i.e. medical or health policy, was by that time an established concept, thanks in particular to the pioneering work of Johann Peter Frank (1745–1772) in the field of social and preventive medicine.] Kerner's report concerned the sometimes fatal cases of poisoning by spoiled liver sausages and blood sausages that he had treated in the years 1814 and 1815 [7].

In older reports (from the year 1753) of illnesses with gastro-intestinal symptoms caused by blood sausages, the fatal outcome was attributed not to the sausage itself, but to the drastic purgatives used in the therapy. However, Kerner and Autenrieth suspected that it was not the smoking of the sausage or an inadvertent contamination with a toxic plant that was causing the poisonings, but a noxious substance formed in the sausages themselves.

In his detailed report of cases of sausage poisoning dating from 1815, Georg Steinbuch used the crude methods of the still young science of organic chemistry in an attempt to identify prussic acid as the cause. However, he was unable to detect prussic acid in the sausages [8].

In the following years, Justinus Kerner (fig. 1) devoted himself to the study of these poisonings, a pursuit which earned him the nickname 'Wurst-Kerner' ('sausage Kerner'). He was supported in his studies by the *Medizinalcollegium* (College of Medicine of Württemberg, an institution with combined academic and political functions) and received a belated 100-Gulden stipend as compensation for his efforts [11]. Kerner is considered to be a typical representative of German medicine of the Romantic period at the end of the 18th century. These physicians worked on the one hand with the new rational scientific methods such as chemistry, physics, animal experiments and vivisection to solve medical questions. On the other hand, as physicians of the so-called 'natural philosophy' school, they linked the results of their research with irrational theories based on philosophical and mystical premises, with the goal of fitting human beings and medicine into a holistic view of the world. Besides his work in medicine, Justinus Kerner also gained acclaim as a romantic poet and (from 1822 onwards) as generous host in the 'Kerner house' in Weinsberg, a place of pilgrimage for poets, researchers and mystics.

Kerner's scientific work on the poison in sausages continued up to 1824. His reports contain impressive descriptions of the disease and detailed research protocols. His later work, e.g. experiments with the fat poison on the skin of the 'Seherin von Prevorst' (prophetess of Prevorst), Friedericke Hauffe, a patient suffering from somnambulism whom Kerner took into his home and cared for, are clearly characterized by mysticism and partly spiritualistic theories [11–13].



Fig. 1. Justinus Kerner (1786–1862), medical doctor and poet of the German romantic period in Württemberg, publisher of the first monograph on poisoning by spoiled sausages, the illness we call botulism today.

In his extensive monograph of 1822 'Das Fettgift oder die Fettsäure und ihre Wirkung auf den thierischen Organismus, ein Beytrag zur Untersuchung des in verdorbenen Würsten giftig wirkenden Stoffes' ('The fat poison or the fatty acid and its effect on the animal organism, a contribution to the investigation of the poisonous material in spoiled sausages'), Kerner also analysed the chemical structure of the assumed 'fat poison' in the sausages. His experimental protocols clearly show the influence of early organic chemistry. In particular, Kerner was looking for acids and alkaline substances. He compared the smell and colour of distillates of well-known substances, e.g. prussic acid, arsenic, Welthersches Bitter or extracts of boiled onions, with the extracts of sausages. Kerner postulated a connection with nitrogenous products, especially Welthersches Bitter. (Welthersches or Weltersches Bitter, also called indigo bitter, is nowadays known under the name picric acid. This substance was discovered in 1799 by

J.J. Welter, 1763–1852, the owner of a chemical factory in Valenciennes, by cooking silk with nitric acid [14].)

Kerner discovered that the poison developed more readily inside sausages that were particularly tightly stuffed. However, he attributed this not to the anaerobic conditions inside the sausage, but rather to the unhealthy meat of the fattened pigs.

Environmental influences on the occurrence of the fat poison, e.g. the strong influence of warmth and electricity (e.g. thunderstorms during the period the sausages were hung up for smoking) are discussed. Kerner assumed a similarity or even a connection of the fat poison with the so-called adipocires (waxes found on corpses) and the Welthersches Bitter and referred to the opening of the Graveyard of the Innocents in 1786 and 1787 in Paris, where approximately 1,500 corpses had been found in a cave, converted into a waxy, greasy mass.

In 1824, another monograph on poisonings by spoiled sausages was published by a medical doctor named Weiss [15], a public health official (Oberamtsarzt) in Bachnang, with a prefix and an appendix by Justinus Kerner, who meanwhile was Oberamtsarzt in Weinsberg. In the prefix, Kerner refers to his newest chemical investigations on the fat poison and tries to confirm his theory that this poison is the result of a chemical reaction between a fatty acid and an alkaloid, probably the Welthersche Bitter.

In his 1822 monograph on the fat poison in spoiled sausages, Kerner also reported his own experiences in taking doses of the diluted poison: it had a sour taste, dried out his mouth and throat and caused choking in the larynx. With higher doses, his eyelids became tired and his vision blurred, he felt a light stinging in the urethra and a dull pain in the abdomen, accompanied by constipation. The palms and the soles of his feet became dry. Carrying out experiments on oneself seems to have played a role in medical research at most times, and such practises were not uncommon at that time – but when Autenrieth, Kerner's medical superior, heard of these experiments, he admonished Kerner not to play with his life [11].

The most conspicuous characteristics of the poison are its paralysing effects on the sympathetic nervous system without affecting the senses. The most common symptoms are dysphagia, paralysis of the intestines, extension of the pupils, double vision, paralysis of the eyelids, hoarseness, thickened mucus, dry palms and soles, desiccated excrement, thickening of the blood with the formation of 'heart polyps' and an intense muscle rigidity after death. These are only some of the many symptoms – right up to the changes in the production of ear wax – Kerner described. It is particularly this accuracy in the description of the clinical symptoms that still impresses today.

Although Kerner stated that the paralysis of the sympathetic nervous system played an important role in the pathogenesis of these symptoms and

even compared the effect of the poison with that of rust interfering with an electric conductor, it would be wrong to conclude that Kerner's ideas corresponded to our present theory of the mechanism of the poison. The term 'sympathetic nervous system' in Kerner's day was used to denote a system that energized all of life's functions by means of an activating 'fluidum' flowing in the nerves. The distinction between autonomous and arbitrary peripheral nervous system, and nerve potentials, the transmission of nerve impulses and neurotransmitters were all discoveries made in the decades after 1820 [16, 17].

In his 1822 monograph, Kerner described 27 animal experiments with cats, rabbits and birds, followed by 24 descriptions of accidental human poisonings by liver sausages and blood sausages. The autopsies of the victims and the animals revealed very few pathological findings. In addition to the paralysis, Kerner paid particular attention to the supposed origin of heart polyps (black, smudgy, thick masses affixed to the muscles inside the heart), which had also been observed in victims of viper poisoning. In Kerner's view, this was evidence that pointed against arsenic as being the agent responsible for the sausage poisonings.

Kerner devoted two chapters to antidotes against the sausage poison, mainly different acids and, more important, alkaline substances. 'Wie dem Arsenik, so wohnt auch hauptsächlich dem Fettgifte, neben der Irritabilität tödtenden eine konstriktorische Kraft inne' ('As with arsenic, the fat poison has – in addition to qualities that kill the irritability – a constricting strength'). Both of these poisons belong to the very slowly working poisons that drain the system. Since sulphur potashes (the so-called 'alkalische Schwefelleber', hepar sulphuris [14]) were effective when the irritability had drained from the muscles due to white arsenic, it was a logical step to try them in the treatment of poisonings with this fat poison. He himself had felt an improvement in the dryness of his throat by using alkaline sulphur during his own experiments with the poison.

In the following section in his monograph, Kerner described concrete therapeutic interventions:

Die erste Hülfe muss man natürlich auch bei dieser Vergiftung in Herauswerfung dieses Giftes aus Magen und Darmkanal suchen, man muss 2–3 Grane Brechweinstein und 20–24 Grane Brechwurzel mit Glaubersalt, in einer geringen Menge Wasser aufgelöst, so bald als möglich reichen. ... Sollte das Schlingen, auch für Flüssigkeiten, schon gehemmt seyn, so müsste man die Heilmittel vermittelst einer Röhre von elastischem Harze in den Magen zu bringen suchen.

(The first aid in this intoxication is to eliminate the poison by expelling it out of the stomach and digestive system. Two to 3 grains of "Brechweinstein" and 20–24 grains of "Brechtwurzel" and Glauber salt, dissolved in a bit of water, must be taken as soon as possible. If swallowing, even of fluids, is no longer possible, the remedies must be brought into the stomach using a tube made of flexible resin.)

Kerner mentions an instrument described by Monro the elder (1733–1817). This is probably one of the first descriptions of the medical use of a gastric tube.

Sollten Zeichen von erloschener Irritabilität drohen, dann würde ich zu abwechselungweisem Gebrauche der Alkalien und Säuren, und zwar der alkalischen Schwefelleber, hauptsächlich äusserlich in Bädern, und des Weinessigs innerlich rathen, und dabei immer noch die peristaltische Bewegung des Darmkanals überhaupt befördernde, eröffnende Mittel, namentlich auch eröffnende Klystiere, fortsetzen lassen.

(‘If the patient fails to exhibit irritability, then I recommend the alternating use of alkali and acids. Alkaline sulphur baths should be used externally and acetic acids internally. In order to maintain the peristaltics of the intestines, repeated enemas are very beneficial.’)

Of special interest are also the remarks about artificial respiration and tracheotomy, since both were uncommon at that time:

Tritt aber bei Zeiten eine Lähmung dieses zum Leben so nothwendigen Organes, der Lunge, ein, so droht schnelle Zersetzung der Blutmasse ohnediess, und dann wäre vielleicht nur noch in künstlichem Lufteinblasen einige Hülfe zu suchen.

(‘Should after a while paralysis of the vital organ, namely the lung, begin, and the impending decomposition of the blood threaten, then only artificial pumping in of air might be able to provide some help.’)

Kerner then refers to animal experiments using tracheotomy and artificial respiration. In the end, Kerner advised against carrying out a tracheotomy on poison victims, in order to avoid causing further injury to the windpipe already damaged by the toxin.

In the work of Weiss [15] from the year 1824, mentioned above, the author also describes experiments he conducted on himself and records the therapies he prescribed in 29 cases of food poisoning. The work gives a good idea of medical therapy of that period. His investigations supported Kerner’s theory that the poison might have a connection with the *Weltersche Bitter*.

In the appendix to Weiss’ book, Kerner expressed his opinion on the eating habits of the time and suggested preventive measures to avoid poisonings with the fat poison, as he already had in the appendix of his own book 2 years earlier. Among these pieces of advice are the following: the meat of sick animals should not be eaten; meat should be thoroughly cooked before further use; copper cooking pots should not be used; pieces of small intestine rather than pigs’ stomach should be used as skin for sausages, and sausages that smell disgusting when cut open should not be eaten [6].

In one sentence he summarizes the whole problem in a statement with a clearly natural philosophical bent:

Allerdings wäre diesem Uebel auf einmal begegnet – würden die Menschen keine Würste mehr speisen; allein dies wird wohl noch so lange geschehen, bis dereinst eine neue Weltkatastrophe, dieses sogenannte kultivierte, Leben aufheben und den der Natur

entgangenen Wurst- und Pasteten fressenden Menschen, zur einfachen naturgemässen Nahrung zurückführen wird.

(‘Of course, this malady could be averted in one fell swoop if mankind would stop eating sausages; however, it will persist until the next catastrophe abolishes this so-called cultivated lifestyle and forces mankind to return to natural food without sausages and pâté.’) [15]

About Fatty Acid as a Possible Therapeutic Agent

With the ever broader spectrum of indications for which botulinum toxin is gaining use as a therapeutic agent, attention has recently turned once again to chapter 8 of the monograph from 1822. The title of this chapter reads: ‘Ueber die Fettsäure, als mögliches Heilmittel’ (‘About fatty acid as possible therapeutic agent’) [6].

Kerner refers to older work on viper poison, in which it was assumed that a ‘wirksames feines flüchtiges Princip’ (effective fine volatile principle) was necessary for life. Viper poison had been used since classical antiquity as a therapeutic agent – in the humoral understanding of pathology – to treat disease-causing imbalances of the body juices. Arsenic was also used as therapeutic agent. Thus, the idea of using a strong poison as a remedy already had a long tradition in medicine.

Kerner states:

Offenbar wirkt dieses Gift [das Fettgift] vor vielen hauptsächlich auf das sympathische Nervensystem lähmend, seine Thätigkeit hemmend, ein. Eine Menge Krankheiten aber heben wir bestimmt nur dadurch, dass wir die so oft durch Nahrungsmittel, Miasmen, atmosphärische Einwirkungen usw. entstandene Aufreizung des sympathischen Nervensystemes hemmen, das in ihm zu sehr erregte Nervenfluidum gleichsam binden.

So sehen wir wohl bei krankhafter Ueberreizung des Lungenerven in der Schwindsucht, die Blausäure, ..., die Digitalis, beim Keuchhusten die Belladonna usw. wirken.

(‘This poison obviously mainly paralyses the sympathetic nervous system, blocking its activity. Many maladies are caused by foodstuffs, miasms and atmospheric exposures that irritate the sympathetic nervous system – these are cured by slowing down and by actually binding the activated nerve fluid. In this way we see the effect of cyanide, ..., and digitalis on the lung nerves in the treatment of kachexia and belladonna in the treatment of whooping cough.’)

Analogously, Kerner believed that the fat poison could be used as a therapeutic substance in the treatment of the following diseases:

Dass in colliquativen Schweissen, ..., vielleicht auch bei zu grosser Schleimabsonderung, z.B. im weissen Flusse, gegen zu stark eiternde Geschwüre, Blutflüsse, usw., dass in faulichten, krebshaften Geschwüren ..., wie der Arsenik und die Chlorine, die Fettsäure anzuwenden wäre, liesse sich, auch der Analogie nach, vermuten.

(‘One suspects that, by the principle of analogy, for excessive sweating, ..., possibly excessive mucous excretions – particularly white mucous – purulent ulcers, chronic bleeding, for putrid and cancerous ulcers, similar to arsenic and chlorine, the fatty acids could be used.’)

Further indications he suggested were the water shyness with rabies, poisonings with viper poison, St. Vitus' dance ('Tanzwut', known today under the name chorea minor), burns and skin inflammations.

The recommendation of using fat poison to protect against contagious diseases such as yellow fever and the plague naturally seems strange from today's infectiological point of view. Behind this advice was the theory that these illnesses were transmitted by predisposition and environmental influences (miasmata), and were therefore more likely to be provoked in persons with a more lively sympathetic nervous system. The restraining, inhibiting effect of the poison was thought to provide protection.

Kerner ends with the following sentence:

Was aber hier über die Fettsäure als mögliches Heilmittel geäußert wurde, gehört allerdings nur in das Reich der Hypothesen, und kann nur von dereinstigen Beobachtungen bestätigt oder widerlegt werden.

('What has been said about fatty acids as a possible remedy is hypothetical and remains to be proven or refuted by observations in due time.')

Nowadays botulinum toxin is indeed used with great success in the therapy of many of the symptoms that Kerner described 180 years ago – although the theoretical background has changed and the poison is not applied as a systemic remedy but exclusively in the form of local injections.

The Discovery of the Bacillus

The Microbiological Age

From the time of these first descriptions, the periodic occurrence of this very dangerous disease has attracted the attention of toxicologists and public health specialists. Apart from the name 'botulism' (lat. *botulus* 'sausage'), the name 'alliantiasis' (gr. *allias*, *allantos* 'sausage') was likewise common.

Initially this term was used only for poisonings by spoiled sausages, later it was also applied to cases caused by spoiled ham. Particularly in the period between 1800 and 1850, many new methods of preserving food were patented. One of the most common was Appert's method of preserving food by cooking in hermetically sealed cans. [François Appert (about 1780–1840) was a cook from the Pfalz region who became a Parisian pastry chef. His food conservation method was developed in 1804 and published in 1810.] These preservation methods caught the attention of military strategists wanting to ensure food supplies for troops at war. A connection between botulism and canned meat was published in 1878. Several Russian publications described a so-called 'Ichthyosismus' following fish consumption and postulated a connection with the toxin of sausage poisonings [3, 18, 19].

The designation botulism became increasingly generalized so that any non-specific disturbances after the consumption of meat, whether the meat was fresh, canned, raw or cooked, from healthy or sick animals, were all named botulism. Current opinion was that poisons from decaying flesh, the so-called ptomaines (choline, neuridine) arising from the enzymatic degradation of meat fats, were responsible for botulism [20].

The Works of van Ermengem

In the year 1897, Emile Pierre van Ermengem (1851–1932), a Belgian professor of bacteriology at the university in Gent, published his work on the discovery of an anaerobe bacterium as the cause of botulism [21].

Despite the variety of pathogenetic theories of botulism at that time, it was clear for van Ermengem that the poison could only be of bacterial origin. This is not so surprising when one considers that he did part of his studies with Robert Koch (1843–1910) in Berlin [22]. After the discovery of bacteria and their toxins as triggers of diseases, and the broad acceptance of these theories thanks to the work of Louis Pasteur (1822–1895) and Robert Koch, the field of bacteriology experienced a tremendous upswing from 1880 onwards. In the following decades, research was vigorous in this field, and new pathogenic bacteria were constantly being discovered.

Van Ermengem carried out his investigations following an epidemic in December 1895 in Ellezelles, a small village in Henegau, in which 3 members of an amateur orchestra had died, 10 had been severely sick and another 10 slightly sick after raw salted ham had been served. After initial symptoms of indigestion, the neurological signs of botulism started: with visual disturbances, abnormal secretions in the nose and throat, hoarseness, cough, dysuria, collapse and dyspnoea, even up to death. The patients remained conscious with their senses intact even until they died.

Van Ermengem examined the ham and the corpses of the victims. He also did animal experiments (fig. 2).

The detailed protocols of the slow death of the animals and the autopsy findings corresponded with the observations, for instance, of Justinus Kerner 80 years earlier. While Kerner described many symptoms that originated in the theories of his time, e.g. the so-called heart polyps or the clumping of dark blood in the heart, the descriptions of van Ermengem particularly concentrated on the modifications to the nervous system.

The results of these experiments showed that the substance van Ermengem was looking for must be, comparable to the already well-known tetanus toxin, soluble and extremely poisonous. It did not develop in the body of the victims, but had to be ingested with the food. The 'active principle of ham poisoning' was susceptible to higher temperatures, but resisted decay.



Fig. 2. Photograph taken by Emile van Ermengem of a bioassay with botulinum toxin: ape III – ingestion of 2 ml maceration.

Above all, van Ermengem noted the fact that there had been another ham stored above the dangerous one in the same barrel, and that this one, although it was also slightly decayed, had not caused any symptoms, while the lower ham, which had been covered in salty water and thus stored under anaerobic conditions, had caused botulism. The two pieces of ham differed only in this one point.

Therefore he wrote:

Höchst wahrscheinlich ist es [das Gift] im Schinken, während der Einsalzungszeit, durch anaerobe Wucherung gewisser spezifischer Mikroorganismen entstanden.
(‘It is highly probable that the poison in the ham was produced during the salting process by an anaerobic growth of specific micro-organisms.’)

The bacteriological investigations on the remains of the ham, the urine samples from the victims, the organs of the corpses and the large number of animals used in his experiments showed that the meat was infected with spores of a larger anaerobic bacillus. Under the microscope he saw a small, poorly mobile, flagellated rod with rounded ends (fig. 3). Under certain conditions, the spores germinated. Van Ermengem was unable to obtain more precise results on the effect of the toxins on the nerves.

The work ends with an ‘important hint’ for prophylaxis:

Die konservierten Nahrungsmittel, welche hauptsächlich der Anaërobie ausgesetzt sind, dürfen niemals in rohem Zustande, sondern stets gehörig gekocht genossen werden.
(‘Conserved food that is kept under anaerobic conditions should never be eaten raw, but only after being thoroughly cooked.’)

In therapeutischer Hinsicht begreift man die Nutzlosigkeit der inneren Anwendung von Antiseptics, wie Resorcin, Salol usw., die häufig empfohlen werden; andererseits hoffen wir auf die Möglichkeit einer serotherapeutischen Behandlung.

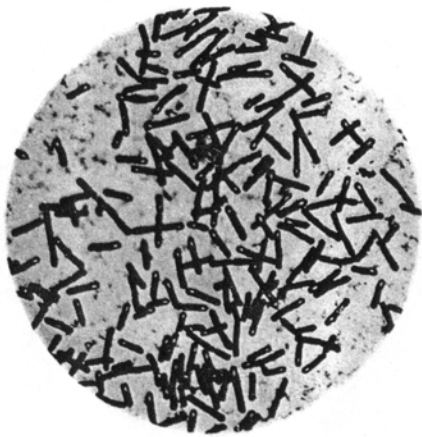


Fig. 3. Microscopic picture from the original work of Emile van Ermengem: *Bacillus botulinus*, 8-day-old culture in sugar gel. $\times 1,000$.

(‘From a therapeutic point of view, the futility of the systemic use of antiseptics such as resorcin, salol etc. can be easily understood, yet we are still looking for a serotherapeutic treatment.’)

In 1904, G. Landmann from the bacteriological laboratories of the chemical factory of E. Merck in Darmstadt examined a series of poisonings caused by canned beans [23]. He also found an anaerobic bacterium whose behaviour in culture corresponded very closely to the bacillus described by van Ermengem. This was the first proven case of botulism following the consumption of canned vegetables.

The Antitoxin

In 1890, Emil von Behring (1854–1917) and Shibasaburo Kitasato (1856–1931) published a paper ‘Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren’ (‘On the building of immunity towards diphtheria and tetanus in animals’). With the discovery of the antitoxins (antibodies) against diphtheria and tetanus, they established the theoretical basis for the development of antiserum therapy. Soon after, the Behringwerke in Marburg began producing large amounts of tetanus and diphtheria antiserum from horse blood.

In the same year as the first description of the *Bacillus botulinus* was published by van Ermengem (1897), Kempner was already able to produce an antitoxin against botulism [24, 25].

In 1910, J. Leuchs from the Royal Institute for Infections in Berlin published a paper on the production of antiserum against the toxin from the *B. botulinus* using horse serum. He had obtained samples of the bacteria from van Ermengem and also from Landmann in Darmstadt [26]. Very important in

Table 1. Strains and sources of *C. botulinum*, arranged according to the date of discovery

Type	First description in the scientific literature	Source of bacteria and biological effects of toxin first described
A	1919, Burke (USA)	food-borne botulism (e.g. bacteria from Landmann 1904; beans)
B	1919, Burke (USA)	food-borne botulism (e.g. bacteria from van Ermengem 1897; ham)
C	1922, Bengston (USA); 1922, Seddon (Australia)	paralysis in chickens (isolated from fly larvae) bulbar paralysis in cattle (' <i>Bacillus parobotulinus</i> ')
D	1928, Meyer and Gunnison (USA)	paralysis in cattle (South Africa)
E	1936, Bier (Ukraine)	food-borne botulism (fish)
F	1960, Moller und Scheibel (Scandinavia)	food-borne botulism (home-made liver pâté)
G	1970, Gimenez and Ciccarelli (Argentina)	soil cultures

this publication was the finding that although the two bacteria and their toxins had similar characteristics, each antitoxin was only effective against the toxin of the same bacterial culture – the heterologous sera had no protective effect. Obviously the two bacterial cultures had produced two slightly different but immunologically distinguishable toxins. Leuchs realized that this would cause problems in the practical application of this antitoxin, since a general practitioner had neither the possibility nor the time to find out which toxin the patient had been exposed to.

The Changing Picture of Botulism

A whole group of further strains of botulinum bacteria have since been discovered, each with an immunologically slightly different toxin (table 1). The name *Clostridium botulinum* was given to these bacteria in 1922 [22, 27].

The first documented outbreak of food-borne botulism in the USA, caused by commercially conserved pork and beans, dates from 1906 [28]. Home canning became popular in America during the time of the First World War. This led to a corresponding increase in botulism and to more intensive research and public information in the 1920s [29].

The foods responsible for botulism differ greatly from country to country and reflect cultural preference in eating habits. In Germany, Poland and France, canned meat is responsible for the majority of poisonings, while in Japan it is mainly preserved fish and in the USA canned vegetables, in particular beans, pepperoni and mushrooms, that are the major sources of botulism [3, 28].

Infant Botulism

Infant botulism was described for the first time in 1976 in the USA. The newly discovered disease was found most often in babies between the age of 2 and 6 months. They showed symptoms of poisoning with botulinum toxin, although no contaminated food could be identified as source. The cause was finally identified to be an opportunistic growth of botulinum bacteria in the intestine. In some cases, spores were found in honey that had been given to the children to soothe them. Age seems to be an important factor in the emergence of infant botulism, since over 90% of the affected babies were younger than 6 months.

C. botulinum only seems to germinate in the intestine when the development of the normal intestinal flora is delayed. In very rare cases has a similar kind of botulism, caused by the growth of *C. botulinum* in the intestine, been described in adults with intestinal anomalies.

After its discovery, 15 cases of infant botulism were reported in 1976 alone. This was interpreted as an indication that the disease could not be all that rare. In the following years, an average of 75–100 cases were reported annually in the USA. In comparison: in the USA there are about 25 cases of food-borne botulism annually, and during the 1970s only 3 cases of wound botulism were reported [2, 3, 29, 30].

Wound Botulism

Back in the first half of the 20th century, it had already been shown that the pathogens of botulism were found ubiquitously in soil. Geographical epidemiological investigations had also been carried out. Thus, similarly to the known infection of wounds by tetanus, it was conceivable that *C. botulinum* might also contaminate and fester in deep wounds; this was indeed proven to be a very rare occurrence. In the period from 1950 to 1985, only 30 cases were reported in the USA. But in the late 1980s, it came to a sudden accumulation of cases of wound botulism in intravenous drug addicts, with 46 cases alone in the years 1988–1995. In 1996, a total of 42 cases were registered in the USA; a correlation with the use of black tar heroin from Mexico was shown. In the meantime, isolated cases of wound botulism in drug addicts have also been registered in Switzerland [2, 5, 31].

Iatrogenic Intoxication

After the first experimental therapeutic application of botulinum toxin in an ape in 1973 (conducted by Alan B. Scott) and successful local therapy in humans with strabismus since 1980, the list of the medical indications for which botulinum toxin can be applied has grown constantly. The toxin is injected locally, but if the dose were high enough, it is conceivable that systemic symptoms could be provoked.

Symptoms of a systemic poisoning with botulinum toxin after therapeutic application were indeed published in 1997. However, a causal relationship between the observed symptoms and the injected toxin is somewhat doubtful, as the dose administered was 10 times lower than the dose theoretically necessary to provoke systemic effects [2, 32].

References

- 1 Abrutyn E: Botulismus; in Fauci AS, et al (eds): *Harrisons's Principles of Internal Medicine*, ed 14. London, McGraw-Hill International, 1998.
- 2 Shapiro RL, Hatheway C, Swerdlow DL: Botulism in the United States: A clinical and epidemiologic review. *Ann Intern Med* 1998;129:221-228.
- 3 Barker WH: Botulism; in Kiple KF (ed): *The Cambridge World History of Human Disease*. Cambridge, Cambridge University Press, 1993.
- 4 Tacket CO, Shandera WX, et al: Equine antitoxin use and other factors that predict outcome in type A foodborne botulism. *Am J Med* 1984;76:794-798.
- 5 Hiersemenzel L-P, Jermann M, Waespe W: Deszendierende Lähmung durch Wundbotulismus. *Nervenarzt* 2000;71:130-133.
- 6 Kerner J: Das Fettgift oder die Fettsäure und ihre Wirkungen auf den thierischen Organismus, ein Beytrag zur Untersuchung des in verdorbenen Würsten giftig wirkenden Stoffes. Stuttgart, Cotta, 1822.
- 7 Kerner J: Vergiftung durch verdorbene Würste. *Tübinger Blätter für Naturwissenschaften und Arzneykunde* 1817;3:1-25.
- 8 Steinbuch G: Vergiftung durch verdorbene Würste. *Tübinger Blätter für Naturwissenschaften und Arzneykunde* 1817;3:26-52.
- 9 Erbguth F, Naumann M: Historical aspects of botulinum toxin: Justinus Kerner (1786-1862) and the 'sausage poison'. *Neurology* 1999;53:1850-1853.
- 10 Müller: Das Wurstgift. *Deutsche Klinik* 1870;4:35.
- 11 Grüsser OJ: Die ersten systematischen Beschreibungen und tierexperimentellen Untersuchungen des Botulismus. *Sudhoffs Arch* 1986;70:167-187.
- 12 Grüsser O-J: Justinus Kerner, 1786-1862, Arzt - Poet - Geisterseher. Berlin, Springer, 1987.
- 13 Schott H: Romantische Naturphilosophie in der ärztlichen Praxis; in Schott H (ed): *Meilenstein der Medizin*. Dortmund, Harenberg, 1996.
- 14 Moeller J, Thoms H: *Real-Enzyklopädie der gesamten Pharmazie*. Berlin, Urban & Schwarzenberg, 1904/1905.
- 15 Weiss: Die neuesten Vergiftungen durch verdorbene Würste, beobachtet an neun und zwanzig Menschen in und um Murrhardt im Königreich Württemberg, nebst dem Versuche einer physiologisch-pathologischen Darstellung der Einwirkung dieses Giftes auf den Menschen. Karlsruhe, Gottlieb Braun, 1824.
- 16 Andral, Bégin, et al (eds): *Universal-Lexikon der practischen Medicin und Chirurgie*. Leipzig, Voigt & Fernau, 1846.

- 17 Schott H (ed): Die Chronik der Medizin. Dortmund, Chronik-Verlag, 1993.
- 18 Birnbaum E, et al: Das neue Buch der Erfindungen, Gewerbe und Industrien: Rundschau auf allen Gebieten der gewerblichen Arbeit, ed 6. Leipzig, Spamer, 1873, vol V: Die Chemie des täglichen Lebens.
- 19 Jaeger H: Die Bakteriologie des täglichen Lebens. Hamburg, Voss, 1909.
- 20 Eulenburg A: Real-Encyclopädie der gesamten Heilkunde, ed 4. Berlin, Urban & Schwarzenberg, 1907, vol I (Aachen-Asphyxie).
- 21 Van Ermengem E: Ueber einen neuen anaëroben Bacillus und seine Beziehungen zum Botulismus. *Z Hyg Infekt* 1897;26:1-56.
- 22 Smith L.: Botulism - The organism, its toxins, the disease. Springfield, Thomas, 1977.
- 23 Landmann G: Ueber die Ursache der Darmstädter Bohnenvergiftung. *Hyg Rundsch* 1904;10: 449-452.
- 24 Behring E, Kitasato S: Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. *Dtsch Med Wochenschr* 1890, Dec 4, No 49.
- 25 Kempner W: Weiterer Beitrag zur Lehre von der Fleischvergiftung: Das Antitoxin des Botulismus. *Z Hyg Infekt* 1897;26:481-500.
- 26 Leuchs J: Beiträge zur Kenntnis des Toxins und Antitoxins des *Bacillus botulinus*. *Z Hyg Infekt* 1910;65:55-84.
- 27 Benedetto AV: The cosmetic uses of botulinum toxin type A. *Int J Dermatol* 1999;38:641-655.
- 28 Foster EM: Reflections on a half-century of foodborne botulism; in Das Gupta BR (ed): Botulinum and Tetanus Neurotoxins., New York, Plenum Press, 1993.
- 29 Black RE Arnon SS: From the Center of Disease Control: Botulism in the United States, 1976. *J Infect Dis* 1977;136:829-832.
- 30 Rick J, Ascher D: Infantile botulism: An atypical case of an uncommon disease. *Pediatrics* 1999; 103:1038-1039.
- 31 Jermann M, Hiersemenzel L-P, Waespe W: Drogenabhängiger Patient mit multiplen Hautabszessen und einem Wundbotulismus. *Schweiz Med Wochenschr* 1999;129:1467.
- 32 Schantz EJ, Johnson EA: Botulinum toxin: The story of its development for the treatment of human disease. *Perspect Biol Med* 1997;40:317-327.

Michael L. Geiges, MD, Department of Dermatology, University Hospital of Zurich,
 Gloriastrasse 31, CH-8091 Zurich (Switzerland)
 Tel. +41 1 255 1111, Fax +41 1 255 4549, E-Mail geiges@derm.unizh.ch