History of Medicine and Ethics

Tetanus: historical and palaeopathological aspects considering its current health impact

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Summary

The present article summarises the historical and palaeopathological evidence of tetanus, an ineradicable yet vaccine-preventable infectious disease caused by Clostridium tetani. The antiquity of the disease is described thanks to historical written sources, artistic references and very recent palaeogenetic data. A recollection of now long-supplanted therapies is offered together with a focus on the introduction of an effective vaccine. Moreover, a potential identification of tetanus in the Bible is analysed and general considerations on the current health relevance of tetanus are presented.

Introduction

The soil provides a biologically active medium rich in microorganisms [1]. Worthy of note is the bacillus *Clostridium tetani*. It is classified as an obligate anaerobic bacterium, which forms spores that can survive in unfavorable environmental circumstances, such as the presence of oxygen. When spores find appropriate conditions for their development, typically an anaerobic environment, they germinate. A wound that is sufficiently deep, as small as that caused by the puncture of a thorn, or a metal spike located in the ground, are sufficient for the tetanus spores to enter the host. Meanwhile, other aerobic bacteria consume the oxygen present in the tissues adjacent to the wound, creating ideal conditions for spore germination. The multiplication of *C. tetani* remains localised in the area of the wound. It is at this stage that the very potent tetanus toxin, also known as tetanospasmin (TeNT, literally the toxin that causes muscle spasms), is released [2]. TeNT binds to the membranes of motor nerve neurons. The nerve impulse that allows voluntary muscles to move is normally regulated by an inhibition phase. The tetanus toxin alters the ability to inhibit the electrical signal, which therefore continues to reach the muscle without any modification. The resulting spasmodic contractions are impressive. The muscles of the jaw contract by tightening the mouth (lockjaw), the forehead is typically wrinkled (tetanic *facies*), and the characteristic sardonic laugh appears on the face [3]. Strychnine poisoning can mimic the contraction of the muscles that gives the impression of a smile [4]. The muscles of the back and the rest of the body, then, contract very conspicuously: one of the most typical postures is *opisthotonos* (Grek ὀπισθεν + τόνος; 'behind'+'tension'), a state of hyperextension where the head, neck, and spine assumes a very arched position [5]. This bodily response was accurately depicted by the famous Scottish neurologist Sir Charles Bell (1774-1842), in 1809 in a patient suffering from this specific tetanic manifestation (Fig. 1). The early form of the disease, the most insidious, leads to premature death, within 5-10 days, usually from asphyxia and heart failure [2].

The Antiquity of Tetanus

Limitations of osteological sources

In the past, and in many less developed regions of the world, tetanus is a real scourge. Besides the typical case of infection contracted following contamination with spores in the soil, two other forms of tetanus should be noted: neonatal, and post-traumatic in soldiers. Neonatal tetanus occurs when the umbilical cord is severed with unsterilised instruments [6]. Estimates from the World Health Organization report 49,000 newborns died in 2013 from neonatal tetanus, a figure that is still staggering, although there has been a substantial reduction since the 1988 picture, when newborn deaths amounted to nearly 800,000 [7]. Post-traumatic tetanus in soldiers is historically well-documented. The death of soldiers caused by traumatic tetanus resulted from a wound sustained in battle. The Roman historian Livy (59 BCE

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Fig. 1. The image depicts a case of tetanic opisthotonos, a condition characterised by a fully arched spinal column, forming a bridge-like conformation. This is caused by a significant contraction of the dorsal muscles, with the extensor muscles of the spine being more prominent than the flexor muscles - 1809, painting by British physician Sir Charles Bell (1774-1842) (Wikipedia Commons – Public Domain).

- 17 CE) remarked on the siege of Sutrium in 309 BCE, during the war between the Romans and the Etruscans (*Ab Urbe Condita Libri*, IX.32): *apud Romanos tantum volnerum fuit ut plures post proelium decesserint quam ceciderant in acie* ("the Romans had so many wounded that more died of their hurts after the battle than had fallen on the field") [8, 9]. Not all battle wounds at the time (as well as in previous and subsequent conflicts) were infected with tetanus spores, but the picture offered by Livius' sentence is quite vivid: the phase *after* the actual battle, not *before* or *during* it, can prove the most problematic for survival.

From a palaepathological perspective, unlike with other infectious diseases leaving pathognomonic traces in the skeleton (*e.g.* tuberculosis, leprosy, and syphilis) it is extremely difficult to diagnose tetanus from bone lesions because they are non-specific [10]. They consist of rib fractures, exacerbated by an individual's bone fragility (either in young individuals or old ones) and compression vertebral fractures, with the spinal segment T4-T6 being the most commonly affected [11, 12]. Compression fractures of vertebral bodies can result in post-tetanic hyperkyphosis [13], yet this is often difficult to distinguish in paediatric patients from Scheuermann's juvenile kyphosis, an idiopathic spinal condition [13]. The only potentially pathognomonic sign could be the division of some vertebrae, as reported in the literature, in two fragments as a result of the tetanic contractions [12], yet these can also be caused by other forms of trauma such as an impact with an object or surface.

Attestations in historical written sources

Referring to ancient texts, the history of medicine and palaeopathological analysis of sources gives interesting clues. One of the earliest descriptions of the disease, particularly of its risus sardonicus and trismus (lockjaw) manifestations, dates back to Ancient Egypt, and is found in the surgical section of the Edwin Smith Papyrus (ca. 1500 BC), in *Case 7* [14, 15, 16]:

> *One who has a gaping wound in his head, which has penetrated to the bone and violated the sutures of his skull, who has a toothache, whose mouth is clenched, who suffers from stiffness in his neck: an ailment for which nothing is done* [15].

Much more accurate expositions are found in Hippocrates' (460 BCE - ca. 370 B.C.E.) work *Epidemics*:

> *The commander of the large ship; the anchor crushed his forefinger and the bone below it on the right hand. Inflammation developed, gangrene, and fever. Her was purged moderately. Mild fevers and pain. Part of the finger fell away. After the seventh day satisfactory serum came out. After that, problems with the tongue: he said he could not articulate everything. Prediction made: that opisthotonos would come. His jaws became fixed together, then it went to the neck, on the third day he was entirely convulsed backward, with sweating. On the sixth day after the prediction he died* [17].

The Roman author Aulus Cornelius Celsus (fl. 1st cent. CE) offered another description of tetanus in his work *On Medicine* (*De medicina*, IV.6):

> *There is, however, no disease more distressing, and more acute, than that which by a sort of rigor of the sinews, now draws down the head to the shoulder-blades, now the chin to the chest, now stretches out the neck straight and immobile. The Greeks call the first opisthotonus, the next emprosthotonus, and the last tetanus, although some with less exactitude use these terms indiscriminately. These diseases are often fatal within four days. If the patients survive this period, they are no longer in danger. They are all treated by the same method and this is agreed upon, but Asclepiades in particular believed in bloodletting […]* [18].

In the above passage, it is worth mentioning how the report that some patients could survive the disease can considered critical since untreated tetanus is *de facto* associated with 100% mortaly. For this reason, it cannot be excluded that cases of spontaneous recovery [19] were observed in antiquity or that, in some instances, tetanus was mistaken for other neurological conditions.

Subsequently, Areteus of Cappadocia (1st cent. CE) in his work *Of the causes and signs of acute diseases* (*De causis et signis acutorum morborum*, I.VI) called tetanus an incurable disease to the point that he went on to write that it is a blessing for the sick person, when the respiratory complications of tetanus arise, they are freed from the pains, the distortion of the limbs and the resulting deformity, a harrowing spectacle especially for family members who witness the scene. Areteus added that the limbs of the tetanus patient are so rigid that even if a doctor wanted to try to loosen them, he or she would have to cut and break them off a person who is still alive. He concluded that the doctor shares the pain and anguish

with his or her patient, being able to assist him or her but not freeing him or her from suffering. For Areteus this condition of helplessness is "the great misfortune of the physician" [20].

The celebrated French surgeon Ambroise Paré (1510-1590) studied trismus and introduced a device to keep a patient's mouth open despite the abnormal contracture: this demonstrate how no-one understood the correct aetiology despite trying to find empirical solutions and how someone could only describe the clinical presentations and outcome with some accuracy.

Finally, regarding the antiquity of tetanus, additional data have recently emerged thanks to palaeogenetic analyses, capable of recovering ancient *Clostridium* DNA from archaeological material; phylogenetic analyses revealed the presence of known clades of *C. tetani*, as well as the identification of new, closely related lineages. Furthermore, 13 variants of the tetanus neurotoxin (TeNT) were identified, including some that were exclusively present in ancient samples from South America. One of these variants was subjected to experimental analysis on mice, which demonstrated that it was capable of causing tetanus muscle paralysis with the same efficacy as modern variants. This finding suggests that ancient DNA may not only serve to confirm the presence of neurotoxigenic *C. tetani* in human archaeological samples, but also to identify new variants of TeNT with the potential to cause disease in mammals. In conclusion, the study of ancient DNA provides insights into the historical evolution of pathogenic bacteria and the possible origin of modern infectious diseases [21].

Tetanus In The Holy Bible?

In the Gospel of Matthew (Matthew 8:5-8 NIV), the following parable is recounted:

> *When Jesus had entered Capernaum, a centurion came to him, asking for help. "Lord," he said, "my servant lies at home paralyzed, suffering terribly." Jesus said to him, "Shall I come and heal him?" The centurion replied, "Lord, I do not deserve to have you come under my roof. But just say the word, and my servant will be healed* [22].

This case was briefly discussed by Kaufamann in a 1964 article [22] who considered the "unusual combination of paralysis with pain" as pointing to tetanus as the illness affecting the centurion's servant. Among Kaufmann's arguments was that strychnine poisoning was not known to have been used at that time, hence making tetanus – or potentially rabies as an alternative – the more likely explanation for the servant's affection [22]. Indeed, as pointed out by Cilliers and Retief [23], strychnine, a toxic alkaloid deriving from the seeds of the small tree *Strychnos nux vomica*, native to India, was discovered only in the 17th century AD. Kaufmann, quoting a 1937 work by Grier dates back knowledge (and/or) usage of strychnine to the 9th century AD, yet still much later than the facts narrated in the Gospels [22, 24]. Rabies, although existing in ancient times, appears less likely a diagnosis because its anxiety, confusion and agitation would have been described by the source (with a potential interpretation as a demonic possession). However, no data are available in this biblical case about previous traumatic injuries sustained by the servant to support tetanus. If one were to consider this a genuine tetanus case and look at it purely in biological terms, he could speculate that it could be an instance of spontaneous recovery from the disease.

Although a rare occurrence, if the tetanus toxin is produced slowly in small amounts, there is time for the host's immune system to produce the antitoxin, which could partly explain cases of spontaneous recovery [19].

One needs to be cautious when reading the Gospels, which shall never beinterpreted as biographies of Jesus Christ. The Gospels are not suitable for palaeopathography since the fil rouge of the entire narrative is the faith in God. In all Gospels, the crucial point is the faith in God. In this case, thanks to the exceptional faith of the pagan centurion, Jesus Christ manifests God's mercy through a miraculous healing (*Then Jesus said to the centurion, "Go! Let it be done just as you believed it would." And his servant was healed at that moment* - [Matthew 8:13 NIV]).

The scientific advances: from *Clostridium tetani* to the first vaccine

The early decades of the 19th century were still far from a significant progress in the medical knowledge on tetanus. On the 8th of October 1838, at a packed session of the Medico-Chirurgical Society of Bologna, the celebrated physician and patriot Luigi Carlo Farini (1812-1866) read a memoir on the use of electricity in the treatment of tetanus [25]. While the treatises on the supposed origin (rheumatic, inflammatory, gastric, *etc*.) of this disease, responsible for an unstoppable muscular contraction almost invariably resulting in the death of the patient, multiplied, the only certainty was the total impotence of the physician.

Inspired by Carlo Matteucci's (1811-1868) experiments on the use of electricity in frogs, Farini had decided to apply a direct current to a patient suffering from tetanus following infection from a gunshot wound. The electric current "giving rise to a kind of paralysis" could "make the tetanic phenomena disappear", leading to a relaxation of the patient, whose muscles finally ended up loosening, including the resolution of lockjaw, as well as the resumption of capillary circulation.

The beneficial effects, unfortunately, were short-lived (about 30 minutes), and the deadly spasmodic contraction returned to take possession of the patient's exhausted limbs. Before long, the unhappy man expired. A disconsolate Farini admitted the defeat of this new therapeutic approach. Nevertheless, animated by a sincere spirit of research and emphasising albeit partial benefits of his method (which nowadays would be called "palliative"), he proudly affirmed:

And let me be told whether other means and drugs give birth to similar advantages, or whether sooner

many are not clearly useless or harmful, and others are worthwhile in dampening sensitiveness for an instant by giving rise to engorgement and thus worsening morbid complications [25, authors' own translation].
Unable to discover the cause of the disease, Farini tried to rationalise the prescribed therapy and spare the sufferer whose fate is sealed from an unnecessary ordeal. The study had a resounding international reach, even appearing in the pages of the British journal *The Lancet*, where 10 years earlier, a similar case had been reported, in which apparently a combination of rectal opium and electricity had saved a woman's life from tetanus secondary to an iatrogenic blisterover the chest [26].
The cause of the disease was not understood until 1884 when Giorgio Rattone (1857-1929) and Antonio Carle (1854-1927), demonstrated the infectious nature of tetanus and its transmissibility in rabbits. Meanwhile the internist Arthur Nicolaier (1862-1942) identified the causative agent as *C. tetani* bacilli. In contrast, the credit for isolating the tetanus germ in the laboratory belongs to Japanese physician Kitasato Shibasaburo (1853-1931). Shibasaburo was also the co-discoverer (with Alexandre Yersin) of the causative agent of bubonic plague (*Yersinia pestis*) during the 1894 epidemic in Hong Kong, which gave rise to the Third Plague Pandemic [27].
With his German colleague Emil von Behring (1854-1917) they actively collaborated [28, 29]. In 1890 they were able to produce the first serum capable of counteracting tetanus toxins. Unfairly, the discovery won the Nobel Prize in 1901 for the German scientist alone.
Passively transferred antitoxin was developed in 1897 by Edmond Nocard (1850-1903) and was used throughout the First World War [28, 29]. However, the first effective active tetanus vaccine was not successfully developed until 1923 by bacteriologist Gaston Ramon (1866-1963). He succeeded inactivating the tetanus toxin obtaining the so-called toxoid or anatoxin and immunitiy in the vaccinated. The gradual development and steady use of large-scale vaccines then allowed a gradual reduction in tetanus mortality.

Tetanus Today

If vaccinations are admnistered, tetanus does not pose a threat today. However, unlike many viruses, tetanus is not eradicable because the spores are prevalent in the environment. News of a case of tetanus in a little girl hospitalised in Turin in October 2017 caused great public apprehension and inflamed the vaccine diatribe [30]. Around the same time, another case was reported in specialist medical literature in France. Interestingly, sometimes a single episode generates stronger emotional reactions than one would expect compared mulitple cases reported all at once. For example, although little has been reported in the press in recent years, there is another, much more extreme scenario in which the importance of tetanus vaccination is decisive: that of natural disasters [31]. Also wars (the current Russo-Ukraine war and the Israelo-Palestinian conflict) are potential conditions for the spread of tetanus (as it was during WWI) and shall be taken into consideration.
Tetanus, along with other infectious diseases, is a major threat following events such as earthquakes, tsunamis, hurricanes, and nuclear disasters. There is no need to go too far back. In 2004, a combination of earthquake and tsunami devastated Aceh in Indonesia over 8 minutes and even reached Thailand, India, Sri Lanka, and all the way to the coast of East Africa claiming the lives of 127,000 people (more by other estimates) and left about half a million injured. Another smaller event in 2006 with around 6,000 dead, and 37,000 injured) followed an earthquake in Yogyakarta, Indonesia. In both these events, tetanus readily manifested itself, with 106 cases documented in Aceh in the months following the earthquake that initiated the tidal wave, and 71 in Yogyakarta [32, 33].
Very significant is one additional case of tetanus reported in the international scientific literature, that of a 66-year-old Hispanic-American gardener who developed tetanus and risked death because the site of entry of the *C. tetani* spores was not obvious to the physicians, other clinical diagnoses initially being considered. The clinic, however, included, quite classically, lockjaw (spastic contracture of the masseter muscles), opisthotonos (spasm of the back muscles along the spine), sardonic laughter (spasm of the facial muscles mimicking a smile), and a boat-shaped abdomen (conformation due to contracture of the abdominal muscles). Once diagnosed with the disease, the patient was saved by a cocktail of drugs: benzodiazepines administered intravenously (anxiolytic action), neuromuscular blockers (to block nerve impulse transmission at the neuromuscular junction), mechanical ventilation (supporting patient breathing by ensuring adequate air volume to the lungs), metronidazole antibiotic therapy (active against vegetative forms of *C. tetani*), tetanus anti-toxin (antibodies that directly counteract the pathogen) [34].
In earlier times this patient would almost certainly have died, while today science has saved him.

Conclusions

Tetanus has been a constant companion of humankind, as evidenced by its presence in ancient texts and recent palaeogenetic discoveries. From a purely palaeopathological perspective, the ancient skeletal remains so far analysed are not particularly helpful in identifying tetanus in the ancient world. The effects of the strong contraction of the back muscles may manifest themselves at the level of the spine as an hyperkyphosis (severe curvature of the vertebral column). However, such condition would not be pathognomonic of tetanus infection, since other diseases manifest a similar skeletal alteration. In contrast, palaeomolecular analyses have identified ancient neurotoxigenic clostridia in samples derived from archaeological contexts.
Notwithstanding notable advancements in medical

science, tetanus persists as a significant public health concern, particularly in regions with limited access to vaccines, with cases emerging in unvaccinated individuals or during natural disasters. In such instances, injuries and a lack of timely medical intervention allow the spores of the bacterium to take hold. The history of tetanus also emphasises the continued importance of vaccination.

Despite the unwarranted scepticism surrounding vaccines, the practice of vaccination remains a pivotal strategy for the control of numerous epidemic diseases, including smallpox (which was eradicated in 1980 as a direct consequence of extensive vaccination programs).

It is regrettable that, as evidenced by the recent SARS-CoV-2 pandemic, mistrust of vaccines has once again become prevalent. This is due to the rapid transmission of disinformation campaigns and fake news via the Internet, and on occasion, the endorsement of misleading information by celebrities.

Vaccine hesitancy and anti-vaccine movements have a long history [35, 36]. The first anti-vaccine league was established in the mid-1850s in the United Kingdom, when there was considerable opposition to a law requiring smallpox vaccination [37]. One notable example of endorsement of vaccine hesitancy can be attributed to the poet and politician and leading exponent of Romanticism, Lord Byron (1788-1824), was openly sceptical of the smallpox immunisation method developed by Jenner in 1749. He went so far as to compare it to questionable medical practices and quackery prevalent at the time [38].

Although tetanus is now uncommon in resource-rich settings, the disease remains a threat to all unvaccinated people, particularly in resource-limited countries where the continued existence of *C. tetani* in the environment indicates that while the disease can be controlled, it cannot be eradicated. Since *C. tetani* spores cannot be removed from the environment, immunization and suitable treatment of wounds and traumatic injuries are necessary for tetanus prevention.

Consequently, ongoing vigilance and vaccination efforts are essential.

Informed consent statement

Not applicable.

Data availability statement

Not applicable.

Conflicts of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

FMG, EV: designed the study; FMG, EV: conceived the manuscript; FMG, EV: drafted the manuscript; RB, STD, VV, AN, MM, EV: revised the manuscript; FMG, EV, RB, STD, VV, AN, MM, EV: performed a search of the literature; RB, STD, VV, AN, MM: critically revised the manuscript; FMG, EV, RB, STD, VV, AN, MM, EV: conceptualization, and methodology; FMG, EV, RB, STD, VV, AN, MM, EV: investigation and data curation; FMG, EV: original draft preparation; MM: editing. All authors have read and approved the latest version of the paper for publication.

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