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History of Tuberculosis

Traces of Tuberculosis in Prehistory

The earliest evidence of tuberculosis (TB) in man and animals is provided by bone finds – mainly fragments of vertebrae – showing the gibbus typical of tuberculous Pott's disease. The oldest examples of spinal TB, in the form of fossil bones, date back to about 8000 BC [1]. A bone from the Neolithic period (ca. 5000 BC), found in the region of Heidelberg, likewise shows evidence of tuberculous changes. Findings in certain Egyptian mummies clearly indicate that spinal caries existed around 2400 BC.

The depictions of a gibbus in statuettes of Ancient Egyptian and pre-Columbian origin represents clear evidence of spinal TB. Lastly, there is the unique bacteriological finding of acid-fast bacilli in smears taken from a psoas abscess in the astonishingly well-preserved mummy of an Inca child from around 700 BC, clearly documenting a case of TB of the lumbar spine [2, 3].

Description of Tuberculosis from Antiquity to the Renaissance

The oldest legal text in the world – formulated by the Babylonian monarch Hammurabi in 1948 and 1905 BC and engraved in cuneiform script on a stone pillar now kept at the Louvre in Paris – mentions a chronic lung disease, which was very probably TB [4].

In Greek literature there appears around the time of Hippocrates (460–370 BC), the most famous of the Greek physicians, the concept of 'phthisis', or consumption. The Hippocratic school described phthisis as the commonest disease of the period, and as a condition that usually culminated in death. Hippocrates also wrote something that no physician would dare to write today: he warned his colleagues against visiting consumptives in an advanced stage of the disease, since the patient would in any case die, thereby damaging the physician's reputation. Patients with phthisis were often nursed in the temple precinct, where they were treated with good food, milk and physical exercise. Hippocrates first observed tubercles ('phymata') in the tissues of cattle, sheep and pigs. Analogous findings in man are not described, since human autopsies were not performed in the Greek world at that time. The Hippocratic school considered pulmonary phthisis a hereditary rather than infectious disease. They also failed to recognize a common entity of tubercles and consumption.

Aristotle (384–322 BC), on the other hand, described 'scrofula' on the skin of phthisic pigs. He believed phthisis to be contagious even though general opinion at the time tended to the alternative theory that the disease was hereditary [5].

In Indian literature we find passages from 1500 BC in which consumption is attributed to excessive fatigue, worries, hunger, pregnancy and chest wounds. No Brahman was permitted at that time to marry into a family that harboured consumption.

From Caelius Aurelianus, a Roman physician of the 5th century AD, we have received a masterly description of the disease, which reveals a clinical knowledge astonishing for the period. He writes: 'The patients suffer from a latent fever that begins towards evening and vanishes

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again at the break of day. It is accompanied by violent coughing, which expels thin purulent sputum. The patient speaks with a hoarse voice, breathes with difficulty and has hectically flushed cheeks. The skin on the rest of the body is ashen in colour. The eyes have a weary expression, the patient is gaunt in appearance but often displays astonishing physical or mental activity. In many cases, wheezes are to be heard in the chest, and when the disease spreads, sweating is seen on the upper parts of the chest. The patients lose their appetite or suffer hunger pangs. They are often also very thirsty. The ends of the fingers swell and the fingernails curve greatly.'

Around the start of the Common Era, Aretaeus of Cappadocia described pulmonary consumption as a disease with purulent, chronic sputum and a generally poor prognosis.

A century later, Galen (131–201), who had no knowledge of morbid anatomy, first suspected the contagious nature of phthisis, clearly preferring this to the hereditary theory of the disease. He therefore warned against intimate contact with consumptives. For many centuries thereafter medical thinking strayed little from Galen's dogma [5, 6].

Reviewing consumption over the course of history, it is clear that upsurges of the disease have always followed the development of new urban structures drawing large numbers of people into a confined space. This was the case with the establishment of the cities of the Nile Valley, in the Greek polis, and in Rome of the early imperial period. The famous 'plague of Justinian' was probably also at least partly due to invasion of the Mediterranean urban cultures by young people from northern and eastern Europe who had never before come into contact with TB. It is in any case noteworthy that this 'plague' lasted throughout the 6th and into the 7th century, while true plague epidemics in later centuries, however devastating they were, always abated again after a few years [7].

This probably also explains why phthisis is not mentioned at all in either the Old or New Testament of the Bible. These writings deal mainly with rural populations not yet gathered into large cities with intensive human contacts [8].

From the Renaissance to the Modern Era

In Renaissance northern Italy, Fracastorius of Verona (Girolamo Fracastoro 1478–1553) reserved the term 'phthisis' exclusively for pulmonary consumption. He stressed that in the hitherto authoritative literature – from the Greek schools to the School of Salerno – the term had been used for 'every manner of wasting'. Fracastorius was the first to postulate, in his work *de contagione*, that phthisis is transmitted by an invisible 'virus', and that it could survive for 2 years in the clothes of a consumptive. He also noted that 'the disease comes from an acquired lung ulcer, from which true pus is discharged'. This mention of a lung ulcer shows that this first major step forward in the description of consumption and its infectiousness is inconceivable without a knowledge of morbid anatomy [4, 6].

The pathoanatomical basis of the disease began to be investigated in the late 14th century, at about the same time that Gutenberg was developing the art of printing. The era of rapid dissemination of newly acquired medical knowledge had thus begun.

While Vesalius (1514–1564), the great anatomist of the Renaissance, studied and described the normal morphology of the human body, other physicians developed the techniques of post-mortem examination and began to correlate the autopsy results with disease symptoms [6].

The 17th century ushered in the era of detailed pathoanatomical description of consumption. In his *Opera Medica* of 1679, Sylvius de la Boë of Amsterdam (1617–1655) was the first to mention tubercles as constant and characteristic lesions in the lungs and other organs of consumptives. He also described their progression to cavities and ulcers. In addition, he identified a syndrome combining phthisis with the skin disease of 'scrofula' – a conclusion echoed 10 years later by Richard Morton (1637–1698) in London. Morton believed that the disease has three stages, initial inflammation giving way to tubercle formation, which ultimately progresses to ulcers and thus to phthisis. He also maintained there were cases that progressed extremely slowly, permitting continued life. Both Sylvius de la Boë and Morton regarded the disease as hereditary, although Morton did not rule out the possibility of transmission by intimate contact [4].

The foremost morbid anatomist of his age, Giovanni Battista Morgagni of Padua (1682–1771), was so convinced of the contagiousness of consumption that he refused to perform post-mortem examinations on consumptives for fear of infection [7].

The Englishman Thomas Willis (1621–1675) described miliary and chronic, fibrotic forms of phthisis, and in 1702 Manget in France devoted an entire work to the phenomenon of miliary tuberculosis. The Italian medical literature of the 17th century provides clear evidence of a belief in the infectious nature of phthisis. In 1699 the Republic of Lucca issued an edict stipulating that 'in

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future, human health must no longer be endangered by objects remaining after the death of a consumptive person'. The names of patients with consumption were also to be reported to the authorities and disinfection measures taken. Physicians were urged to perform autopsies on persons who had died of phthisis [9].

In 1720, the English physician Benjamin Marten (1704–1722), in his book *A New Theory of Consumptions, More Especially of a Phthisis or Consumption of the Lungs,* which became really well known only 150 years later, voiced the suspicion for the first time that the disease might be caused by small living creatures which, once they had gained entry to the body, could produce the lesions and symptoms of phthisis. Marten knew about the first microscopes and this probably suggested the idea that the small protozoa and other organisms seen by the first microscopists in water droplets could be responsible for tuberculosis. He goes on to state in his work: 'The disease may be transmitted by inheritance, perhaps even in the womb, but also by contact from person to person. Occasional association with an infected person is harmless by contrast, for example, to smallpox, but continued contact is dangerous. This in particular for persons with constitutionally limited resistance, especially if they are the children of phthisic parents. Frequent eating and drinking with a phthisic or conversation with him at a distance so short that part of his expired air can enter the lungs of the healthy person, may produce the disease in that person.' For that time, a truly astonishing epidemiological insight [4, 9]!

This was the state of knowledge by the end of the 18th century, at which time the foundations for the ultimately decisive discoveries of the 19th century were laid with the development of microscopy.

The Single Disease Entity of Tuberculosis

It is impossible to speak of TB research in the strict sense before the start of the 19th century. It is therefore also only from this point onwards that firm data can be found on pumonary phthisis. The voyage of discovery began with discussions on the infectiousness and unitary nature of the disease. The most prominent unitarians, building on the ideas of Sylvius de la Boë and Morton, were the Frenchman René Théophile Hyacinthe Laënnec in Paris (1781–1826) – inventor of the stethoscope and mediate auscultation – and the Viennese anatomist and pathologist Carl von Rokitansky (1804–1878). By contrast, Giovanni Battista Morgagni in Padua (1682–1771), and later even Rudolf Virchow in Berlin (1821–1902), clung until death to the notion of differing entities of scrofula, tubercles and phthisis. In his *Systematik der speziellen Pathologie und Therapie,* Johann Lukas Schönlein of Würzburg (1793–1864) listed scrofula, tubercles and phthisis as separate diseases under the heading of 'haematoses'. In 1834, he coined the term 'tuberculosis' to describe affliction with tubercles. However, he did not recognize its oneness with scrofula and phthisis [7].

Proof of the Infectiousness of Tuberculosis

The positions taken by these 'opinion leaders' on the aetiological unity versus distinctness of the various forms of TB divided them along quite different lines from the debate as to its tumorous versus infectious nature. For example, the unitarian Laënnec regarded phthisis as a tumorous disease like cancer, and Rokitansky denied it was infectious. Even more ironically, Philipp Klencke of Berlin (1813–1881), who in 1843 became the first to demonstrate the transmissibility of TB experimentally, nevertheless considered the disease a tumour. In two experiments, Klencke injected material from a tubercle into rabbits intravenously and the animals died of generalized TB.

A year later (1844), Jakob Henle (1809–1885) in Göttingen conjectured that phthisis could be contagious: '... under certain circumstances, ... where there is a more or less marked predisposition'. Here he penetrated to the heart of the matter. Today, 150 years after Henle, we know that no more than 10% of people infected with TB actually become ill. Henle also reported on a woman with consumption whose cat had died of the disease. In 1840 Henle advanced three postulates for proving the infectiousness of a disease: (1) the causative agent must be found in every case of a disease; (2) it must not occur in another disease, and (3) its application must always provoke the same disease [9].

Leopold Auenbrugger (1722–1809), originator of the percussion technique, published his work *Inventum novum ex percussione thoracis humani interni pectoris morbos detegendi* in Vienna in 1761, after many years of comparing percussion findings in the living with later autopsy results. It struck him that young men from the country arriving in the city for military service often fell ill with consumption. This he explained by sadness brought on by loss of freedom and homesickness. However, it was not melancholy but the roommate with open TB that infected the young recruits.

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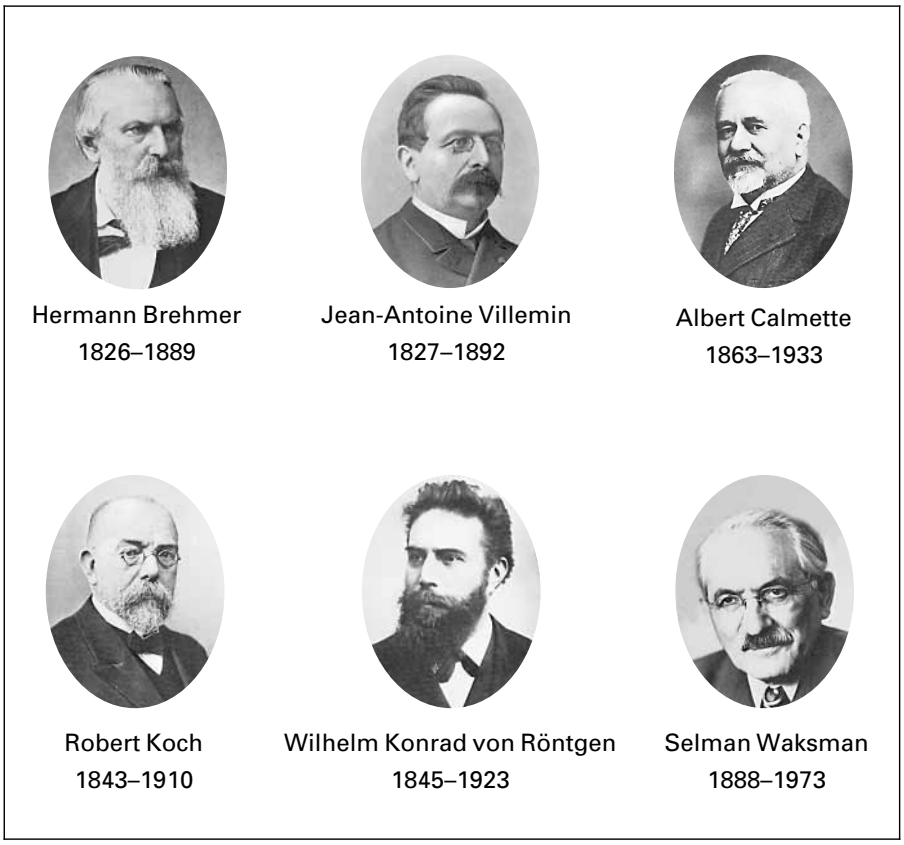

Fig. 1. Pioneers of tuberculosis research.

Tuberculosis Research in the Modern Era

In his pioneering work, *Cause et nature de la tuberculose: son inoculation de l'homme au lapin,* published in 1865 in the Comptes rendus de l'Académie des Sciences, the French military surgeon Jean Antoine Villemin (1827–1892) single-handedly demonstrated that phthisis from humans or cattle could be transmitted to rabbits or guinea pigs. Blood or sputum from tuberculous rabbits, injected into other laboratory animals in controlled experiments, produced full-blown tuberculosis, whereas analogous transfer of cancerous or fibrotic tissue had no effect on the recipients. In the light of this monumental discovery, he postulated for the first time that the disease is caused by a specific microorganism, which must be present in the air. In military style he drew the conclusion that 'the phthisic soldier is to his roommates what a glandered horse is to its stablemates' [7, 9].

However, the microbe itself at first still stubbornly held on to its secret. In 1877, Theodor Klebs (1834–1913) succeeded for the first time in keeping the causative agent of tuberculosis alive on protein in artificial cultures, and then using it to produce the disease in laboratory animals. But even he failed to recognize the true nature of the organism.

This major achievement of bacteriology was left to Robert Koch (1843–1910), a pupil of Henle's. As a gifted microscopist, he produced irrefutable evidence in 1882 that a specific microbe is the fundamental cause of tuberculosis. At a dramatic lecture delivered to the Physiological Society at the Charité Hospital in Berlin on 24th March 1881 under the title *Die Ätiologie der Tuberkulose,* he demonstrated for the first time the bacteria that Villemin and later Klebs had sought for so long in vain. Using special staining techniques he succeeded in visualizing slender rods – which he called tubercle bacilli, *Mycobacterium tuberculosis* – within the tuberculous tissue. At first Koch was unable to culture the demonstrated bacteria, get them to grow again in a laboratory animal and finally close the chain of evidence by histological examination of the resulting tuberculous tissue. However, he then used Tyndall's method of sterilizing ox and sheep serum at 58°C and coagulating it at 65°C. On such culture media he was finally able to follow the growth of the

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microbe with a magnifying glass as a delicate, filmy layer. Microscopic preparations of this film yielded pure cultures of the bacteria, which, when inoculated into laboratory animals, led to the development of tuberculosis. Robert Koch had thus fulfilled the postulates of his teacher, Henle. The listening scientists followed this demonstration in rapt silence. Paul Ehrlich, the future inventor of Salvarsan, the first antisyphilitic agent, wrote later: 'This evening remains imprinted on my memory as the most awe-inspiring scientific event I have ever attended.' The event was immediately recognized by the world as what it truly was – a milestone and harbinger of a new era for the study and control of the disease. What electrified the world was not so much the scientific brilliance of Koch's discovery as the certainty that man could now really begin the struggle against the most powerful enemy of human life. This enemy no longer remained a phantom but had now finally become visible as a living object. In Europe and America, Koch overnight became the pope of medical science; in Japan a shrine was dedicated to him as a demigod [1, 9].

In fact, Paul Clemens von Baumgarten in Tübingen had already seen the tubercle bacillus shortly before Robert Koch – as an unstained bacillus visualized in the caseating tissue by brightening with dilute sodium hydroxide. However, Baumgarten's paper appeared only some weeks after Koch's famous lecture at the Charité in Berlin.

Subsequently, Robert Koch was elected to the Imperial Health Office in Berlin. He surrounded himself with such outstanding colleagues as Georg Gaffky and Friedrich Löffler, and went on to further important discoveries in bacteriology, identifying in turn the causative agents of typhoid fever, glanders and diphtheria.

However, his special interest in TB remained. For example, he demonstrated in the guinea pig various reactions in the wake of secondary and primary infection (Koch's phenomenon). He produced a glycerin extract of dead tubercle bacilli, which was initially named 'lymph' and later 'tuberculin'. Evidently, the composition of the extract was at first kept secret, probably as a result of political pressure, although tuberculin was promoted as an effective remedy. This excited worldwide interest and prompted innumerable TB patients to travel to Berlin in search of a cure.

In fact, tuberculin eventually proved to be of no therapeutic value. On the other hand, as the tuberculin skin test it was of enormous importance in identifying individuals infected with TB, and for this Koch was awarded the Nobel Prize in 1905 [10].

Another equally important contribution to the diagnosis of TB came in 1895 in the form of a revolutionary advance in the field of physics, namely the discovery of X-rays by Wilhelm Conrad von Röntgen (1845–1923). With the aid of the rapidly evolving radiological technique (radiographs of chest and skeleton, fluoroscopy, photofluorography, tomography), the development, course and severity of TB could now be accurately monitored and studied [11].

The present phase of slow eradication of TB in the developed countries of the world would be virtually unthinkable without Röntgen's and Koch's outstanding scientific achievements.

The Development of Tuberculosis Treatment

The scientific medicine of the 19th century was characteristically interested in the description, pathogenesis and diagnosis of diseases, but rarely in their treatment. Laënnec and Villemin, for example, still considered TB completely incurable: 'Presque tous les hommes de l'art pensent aujourd'hui que l'affection tuberculeuse est, comme les affections cancéreuses, absolument incurable' (Laënnec).

Sanatorium Treatment

Then, around the middle of the 19th century, Hermann Brehmer appeared with his thesis: *Tuberculosis primis in stadiis semper curabilis.* He explained it was only necessary to bring the patients to an 'immune place', where the disease would heal by itself. He defined an 'immune place' as a region where there were no known consumptives. He found such a location in a valley in the Sudeten Mountains of Silesia, and in 1856 founded his sanatorium in Görbersdorf in the belief that even existing consumption would abate in an immune place. A place he considered particularly immune was Kirghistan, because it was free of TB: this was a false deduction. We now know that after TB had been introduced there, this and other areas of Central Asia are among the regions with the highest incidences of TB in the world [7, 12, 13].

The discovery of the causative agent of tuberculosis in 1882 gave considerable impetus to these incipient treatment approaches. The next important sanatorium in Germany was established in 1876 by Brehmer's pupil Peter Dettweiler at Falkenstein in the Taunus Mountains. This was followed by St Blasien in 1881, Schömberg in the

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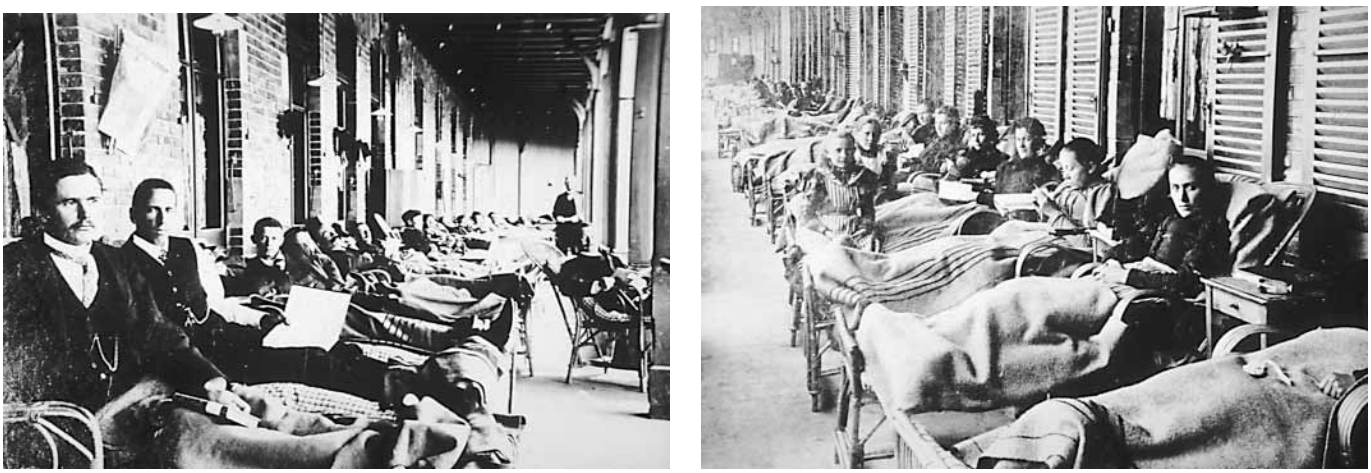

Fig. 2. Typical set-up of the TB patients spontaneously recovered from TB (left: male ward; right: female ward) in the fresh mountain air at the Swiss Alpine Clinic (Heiligenschwendi, 1900).

Black Forest in 1888 and Bad Honnef near Bonn in 1893. Unlike Brehmer, Dettweiler – a former Prussian army doctor who himself suffered from TB – instituted a strictly regulated regime. He introduced a strict rest cure, and invented the since characteristic sanatorium deck chair, as well as a pocket spittoon (popularly known as 'Blue Henry'), although he did not accept that *Mycobacterium tuberculosis* was the cause of the disease. Rather he considered it a parasite that colonized tuberculous tissue. In Switzerland, sanatoria were established in high mountain valleys, such as Davos, Leysin and Montana, in Italy at Sondalo and Valtellina, and in France on the Plateau d'Assis in the Savoy Alps, but also by the sea, as at Berck sur Mer. They all quickly adopted the strict rest cure regime. There has been much debate on the benefit of the sanatorium treatment. However, it certainly contributed to public health by removing infectious consumptives from their normal surroundings. At the same time, the enforced rest, together with a sensible diet and the regulated life of the sanatorium, encouraged the self-healing tendency of consumption in some patients to an astonishing degree [13, 14].

Although patients recovered surprisingly well during sanatorium treatments, the long-term results were fairly depressing. American statistics show that over 60% of patients discharged from sanatoria died of their disease within 6 years. This included 17% of 'cured', 51% of 'stabilized' and 72% of 'improved' TB patients [1].

Since sanatorium treatment was expensive, efforts were soon underway to make such measures available to the most severely affected, socially weak sectors of the population. The term 'Volksheilstätten', or People's Clinics, was coined to describe the fruits of these endeavours. In 1888, a Sanatorium Association was founded in Hanover for the purpose of establishing People's Clinics.

The dynamics of this sanatorium movement eventually led on November 21, 1895 to the setting-up in Berlin of a 'German Central Committee for the Establishment of Clinics for Consumptives'. Its tasks were: (1) establishment of TB sanatoria; (2) provision of economic and hygienic assistance to consumptives; (3) promotion of science and research in the field of tuberculosis, and (4) public education.

Through the initiative of the first General Secretary and actual founder, Gottfried von Pannwitz, the first major scientific congress on combating the public health problem of tuberculosis was convoked in Berlin in 1899. This attracted 2,000 participants, including 200 members of foreign governments. Following the congress the tasks of the Central Committee multiplied to such an extent that in 1906 it was renamed the German Central Committee to Combat Tuberculosis (DZK). After the First World War this was superseded by the International Union Against Tuberculosis (UICT), which held its first conference in Paris in 1920. The German Central Committee became one of its members. After the Second World War the International Union Against Tuberculosis (IUAT/UICT) was reconstituted in Paris in 1946. Since 1986 it has extended its activities to other lung diseases and lengthened its name to the International Union Against Tuberculosis and Lung Disease (IUATLD) [7].

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The Fight against Tuberculosis in the USA

In the 1870s the European TB clinic movement and hygiene campaigns also began to gain ground in the United States, at first hesitantly, but then in leaps and bounds. In 1875, Joseph Gleitsmann from Bavaria established the first mountain sanatorium for chest diseases at Ashville, North Carolina. However, it was Edward Livingston Trudeau who became known as the main driving force behind the spread of the sanatorium concept. He himself had TB and noticed tha this health improved considerably during a prolonged stay in the Adirondack Mountains of New York State [15]. In 1884, he built himself a cabin in which to convalesce at Saranac Lake, a small village at the time. However, shortly afterwards he adopted the sanatorium ideas of Brehmer and Dettweiler, and likewise instituted the strict rest cure at his clinics on the European model [16].

The next few years saw the development in America of organizations for combating TB similar to those already existing in Europe. In 1892, the Pennsylvania Society for the Prevention of Tuberculosis was founded by Lawrence F. Flick in the belief that public health is the responsibility of the government [17]. Ohio and New York soon attached themselves to this movement, which ultimately led to the foundation of the American Lung Association and American Thoracic Society at a joint conference at Atlantic City in 1904. As in Europe, the symbol of the movement was the double-barred cross of Lorraine, the historical emblem of the crusades of the Middle Ages. From this point onwards the organizations for combating TB and the scientific study of the disease for the time being followed largely parallel courses in Europe and the USA [2, 12, 13].

Collapse Therapy: Pneumothorax and Thoracoplasty

In the 1930s, pure sanatorium treatment, with its discouraging long-term results, was gradually supplemented by collapse therapy, leading to a marked improvement in long-term results. That lung collapse could aid the recovery of a tuberculous cavity had been suggested as early as 1771 in an article by Edmond Claude Bourru, librarian of the Faculté de Médecine in Paris [1]. In the early 1800s, there were various reports of symptomatic improvement in TB patients after pleural effusions and spontaneous pneumothorax. In 1888, Carlo Forlanini of Pavia created the first artificial pneumothorax by filling the pleural cavity with nitrogen, and over the next 18 years he published successive results on 25 treated cases [18]. Quite independently, John Benjamin Murphy of the Cook County Infirmary in Chicago observed that unilateral pneumothorax resulting from chest injuries sustained in the Civil War very rarely caused breathing difficulties. In 1898, he published descriptions of pneumothorax produced by trocar, and was probably the first to use the new X-ray technique to dose the size of the lung collapse.

In 1908, Christian Saugmann in Germany then introduced the pneumothorax needle with closing tap and protruding blunt obturator, together with the twin-bottle pneumothorax apparatus with manometer, a simple system that greatly simplified pneumothorax induction, transforming it into a safe routine procedure [19].

In 1925, Amberson and Peters [20] reported on their experience with pneumothorax therapy from 1911 to 1925 at the Loomis Sanatorium in the New York Catskill Mountains.

Over the next 25 years, the pneumothorax technique became the most frequently practised adjunct to the rest cure. If the lung was sufficiently collapsed, the lung tissue relaxed, the cavity decreased in volume, its walls came together, and very often the supplying bronchus became kinked – mechanisms that explain why collapse therapy, despite having otherwise little effect on the tuberculous process, so often led to disappearance of bacilli from the sputum [21].

Occasionally, however, the lung cavities were prevented from collapsing by cord-like adhesions between the two pleurae. This problem was partially solved by the invention of the thoracoscope by Jacobaeus in 1912. Using thermocautery, the fibrous cords could be divided inside the pleural space under direct vision without opening the chest cavity (intrapleural pneumolysis) [22].

In 1933, Banyai in the USA noticed a considerable improvement in a patient's pulmonary lesions after he had accidentally injected air into the peritoneal cavity while replenishing a pneumothorax. This chance discovery eventually led to the establishment of pneumoperitoneum as an accepted treatment method, particularly for cavities in the lower lung fields. The procedure was often combined with exposure and crushing of the phrenic nerve in the right supraclavicular triangle. The resulting temporary diaphragmatic elevation often caused the cavities to collapse, with subsequent disappearance of tubercle bacilli from the sputum, but carried the risk of impaired lung function if the normal movement of the diaphragm failed to return.

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Patients with extensive or complete pleural adhesions close to upper-lobe cavities were sometimes treated in the 1940s by extrapleural pneumothorax, the surgical creation of a space between ribs and adherent pleurae in the neighbourhood of the cavities. This space was usually kept open by 'plombage' with paraffin wax, oil or even Perspex balls. However, because of its many complications, this procedure was eventually abandoned [23].

By contrast, a highly successful measure in the event of failed pneumothorax therapy was thoracoplasty, the surgical procedure of unilateral partial rib resection to reduce the volume of the thoracic cavity. The method originated with Max Schede in Germany, who first performed it in 1890 [24]. The scope of the rib resection was varied according to cavity localization, and the periosteum of the partially resected ribs spared to preserve the stiffness of the thoracic cage following surgery, a consideration of supreme importance for the respiratory mechanics [23, 25, 26].

As an extrapulmonary procedure, thoracoplasty produced consistently good results. With good technique, operations in cavitary TB could achieve closure of the cavities with conversion to negative sputum, well-preserved lung function and low operative mortality in about 80% of cases.

By contrast, prior to the introduction of antituberculous drugs, intrapulmonary operations such as lobectomy, segmentectomy and decortication were beset by numerous complications, including tissue infection, extension of the TB, fistula formation and empyema. As soon as streptomycin became available, all these operations enjoyed a brief renascence and were performed frequently for a few years, until long-term studies clearly showed that complete sterilization of all tuberculous lesions could be achieved without surgery by drug treatment alone. With this the era of surgical treatment of pulmonary TB by pneumothorax and thoracoplasty had effectively come to an end [23].

Tuberculosis Prevention by Vaccination

Attempts to vaccinate against TB date back to well before the discovery of antibacterial drugs. Thus, the Frenchmen Calmette and Guérin were able to show in the early 1900s that after 231 passages through a culture medium containing glycerin and ox bile, a particular strain of *Mycobacterium bovis* (bacille Calmette-Guérin) could no longer produce progressive tuberculous lesions in laboratory animals [27].

BCG immunization was first carried out in Paris in 1921, particularly in children at high risk of infection, and soon became popular throughout the rest of Europe [28]. Any side effects also vanished after the introduction of the intracutaneous vaccination technique. However, in 1930, this method suffered a major setback when 240 children in Lübeck were inadvertently vaccinated with virulent tubercle bacilli, 73 dying of the disease [29]. Nevertheless, by 1945, BCG vaccination was again in use, even in Germany. For a long time, opinions vacillated greatly as to its prophylactic effect. On the one hand, it was seen that in European countries that had stopped BCG vaccination because of the Lübeck catastrophe, tuberculosis was again on the increase in children. It also emerged that BCG in children virtually abolished the most dangerous forms of the disease, such as miliary TB and meningitis. On the other hand, the benefit of vaccination in adults remains a subject of debate. BCG is considered one of the safest of all vaccines, except in immunosuppressed individuals, who may develop local or disseminated bovine TB.

Prevention by Combating Bovine Tuberculosis

In the USA the dangers of bovine TB had been clearly grasped even before the turn of the century. In 1900, seventeen states required negative tuberculin tests for all imported cattle. In 1908, Chicago introduced compulsory pasteurization of milk. In 1917, a tuberculin mass testing program was begun for cattle herds in the USA [30, 31]. By contrast, research in Germany at first focused exclusively on the spread of TB from man to man, not on its transmission to humans in the milk of infected cattle. This was based on a fateful error by Robert Koch, who regarded *Mycobacterium bovis* as nonpathogenic to man.

As a result, no systematic examination of this question was undertaken in Europe before the end of the 1930s. It then emerged that infection by the gastrointestinal route was quite common, infected cow's milk being implicated in 30% of all TB cases in Kiel, 10% in Berlin but only 2% in Vienna. At the time it was still customary in Vienna to boil milk before use [1].

In the early 1950s, regulations were introduced – in the face of considerable opposition from farming circles – requiring the systematic slaughter of tuberculin-positive cattle herds. Thanks to these measures the problem of gastrointestinal TB today no longer exists [32].

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Modern Drug Treatment

Then, in the middle of the Second World War, came the final breakthrough in the treatment of tuberculosis in the shape of antibiotics and synthetic antituberculous drugs. All therapeutic measures employed against TB until then had at best been able to strengthen and support the human body in its resistance to the tubercle bacilli. However, a direct attack on the bacilli had never been possible. While drug treatment of nontuberculous infections had begun some years earlier with the introduction of the sulphonamides and penicillin, these substances proved ineffective against the tubercle bacilli or, in the case of high-dose sulphonamide therapy, too toxic. Therapeutic attempts with gold salts, by analogy with the treatment of rheumatic diseases, were soon abandoned due to lack of success and excessive toxicity [33].

The idea of antibiotic treatment of bacterial infections was in itself by no means new. In 1885, three years after the discovery of the tubercle bacillus by Robert Koch, the Italian Cantani reported loss of virulence in tubercle bacilli under the effect of decomposition processes in human corpses. From this observation Cantani, in a remarkable deductive step, arrived at the idea of treating cases of cavitary pulmonary TB with inhalations of nebulized liquid pure cultures of *Bacterium Termo*, a common saprophytic microbe. The result was a rapid reduction, and ultimately disappearance, of the tubercle bacilli from the sputum, abatement of fever and a marked improvement in the patient's general state. In 1888, Victor Babès in Rumania observed that the metabolic products of various saprophytic microorganisms, such as staphylococci and *Bacterium prodigiosum,* inhibited the growth of tubercle bacilli, whereas streptococci and pneumococci appeared to promote it. Thus, as this early point in the history of bacteriology, clear light was shed on a very important – though repeatedly overlooked – factor in the treatment of TB, namely the significance of the surrounding microflora. Finally in 1913, Vaudremer showed that cultured tubercle bacilli lost their infectivity if they were brought together with culture filtrates of the mould *Aspergillus fumigatus.* Rabbits immunized with tubercle bacilli treated in this way developed only mild, nonlethal disease on massive infection 1 month later with fully virulent tubercle bacilli. These few facts should suffice to show how close researchers had come before the First World War to solving the problem of antibacterial therapy with antibiotics.

However, what was needed for the final scientific breakthrough was the brilliance and persistence of a man like Selman Waksman, who had been systematically studying soil fungi and bacteria since 1914, and at the University of California around 1939 discovered the strong inhibitory effect of certain soil fungi, particularly of the actinomycete gourp, on bacterial growth. From cultures of such soil fungi Waksman and his team in 1940 succeeded in isolating an antibiotic, actinomycin, although this was far too toxic for therapeutic use in animals or man. The same obstacle confronted the practical use of a further antibiotic produced in 1942, streptothricin. Ultimate success came only in September 1943. Cultures of another actinomycete, *Streptomyces griseus,* yielded an antibiotic – streptomycin – that combined maximum inhibition of the tubercle bacillus with relatively low toxicity in laboratory animals. For his outstanding scientific achievement Waksman was honoured in 1952 with the Nobel Prize [34].

One event then succeeded the other with breathtaking speed. Feldman and Hinshaw, two physicians at the Mayo Clinic in Rochester, first tested the antibiotic in laboratory animals infected with TB, and found that it was indeed able to suppress the growth of the tubercle bacilli almost completely in the living organism. Then on November 20, 1994, the step was taken that would lead to the victory of man over one of his deadliest enemies – the use of streptomycin in a severely ill TB patient. Pfuetze, working in collaboration with Feldman and Hinshaw, administered five 2-week courses of streptomycin to a 21-year-old woman over a period of 15 months. The success was overwhelming. The rapidly progressive disease was evidently halted, the bacilli disappeared from the sputum, and the patient speedily recovered. After 10 years of follow-up she was still completely healthy, had married and had given birth to three healthy children.

In Switzerland the first batches of streptomycin became available only after the war, in 1946 and 1947. At the time I was a young intern at a TB clinic in Davos. I shall never forget the indescribable joy we all felt when, for the first time, a patient with tuberculous meningitis – a disease that until then invariably culminated in death within 3 weeks – recovered after intensive treatment with streptomycin. The new drug was certainly not without significant side effects, mainly affecting the auditory and vestibular systems. But the fact remained: the tubercle bacillus was no longer a bacteriological exception; it could be attacked inside the human body and forced to retreat.

A rapid succession of anti-TB drugs appeared in the following years. These were important because with streptomycin monotherapy, resistant mutants began to appear within a few months, endangering the success of antibiot-

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Table 1. Chemotherapy protocol for the treatment of TB

Initial phase (2 months)	
Isoniazid	5 mg/kg/day (max. dose 300 mg/day)
Rifampin	10 mg/kg/day (max. dose 600 mg/day)
Pyrazinamide	30 mg/kg/day (max. dose 2 g/day)
Ethambutol	15–25 mg/kg/day (max. dose 2 g/day)
Consolidation phase (4–6 months)	
Isoniazid	daily, as above
Rifampin	daily, as above
or	
Isoniazid	twice a week 14 mg/kg (max dose 1 g/day)
Rifampin	twice a week 10 mg/kg (max. dose 600 mg/day)

First-line drugs are isoniazid, rifampin, ethambutol, pyrazinamide and streptomycin.

ic therapy. However, it was soon demonstrated that this problem could be overcome by using combinations of two or three drugs.

Following streptomycin, *p*-aminosalicylic acid (1949), isoniazid (1952) pyrazinamide (1954), cycloserine (1955), ethambutol (1962) and rifampin (rifampicin; 1963) were introduced as anti-TB agents. Aminoglycosides such as capreomycin, viomycin, kanamycin and amikacin, and the newer quinolones (e.g. ofloxacin and ciprofloxacin) are only used in drug resistance situations. Combinations of a β-lactam antibiotic with a β-lactamase inhibitor enhance treatment effectiveness, but the newer drugs, including the macrolides, have not received much clinical testing.

Two properties of anti-TB drugs have proven to be important: their antibacterial activity (highest with isoniazid, rifampin and streptomycin) and their capacity to inhibit the development of resistance (isoniazid, rifampin and ethambutol are the most effective). Table 1 outlines the current standard chemotherapy protocol for TB in industrialized nations.

The single exception to multidrug antituberculosis chemotherapy is the isoniazid chemoprophylaxis programme aimed at preventing overt disease by the single-drug treatment of subclinical ('latent') TB. The programme was tested in large cooperative studies, first with children by the US Public Health Service in 1955 and subsequently in adults, with excellent results throughout.

With these or similar dosing schedules there should be rapid clinical improvement and a significant fall in the bacterial count. After a month the patient should be afebrile, feel well and have gained weight. Coughing and sputum should have diminished and improvements show up on the X-rays. Although bacteria will still be present in the smears, they will be difficult to culture. X-ray improvements will continue for 3–4 months. However, if the disease was originally very severe, the endpoint may not be reached for a year.

The absence of radiological improvement in the first 3 months should be reason for concern and indicates that a change in therapy is needed. Patient compliance and the pathogen's drug sensitivity should be reevaluated. Relapses usually occur within 6 months of the end of treatment, and in most cases are due to poor patient compliance; this must be rigorously monitored during subsequent treatment.

When TB becomes active again in a previously treated patient, there is a high chance the bacteria will be drug-resistant. Any current therapy must be suspended until two drugs are found to which the pathogen is fully sensitive, and treatment can be resumed with these. If the microorganism is resistant to the standard drugs, more toxic compounds – such as ethionamide, prothionamide, pyrazinamide, cycloserine, capreomycin, viomycin or kanamycin – will have to be given.

The Significance of the Recent TB Upswing

Worldwide, the recorded number of new cases of TB correlates with economic conditions, the highest incidences being seen in those countries of Africa, Asia and Latin America with the lowest gross national products. The World Health Organization estimates that 8 million people develop the disease each year – of whom 95% live in the third and fourth worlds – and 3 million die of it.

In industrialized nations, including Europe, the steady drop in TB incidence began to level off in the mid-1980s and then stagnated or even reversed somewhat. In the late 1980s, Denmark reported a 10% increase, Switzerland 26%. Much of this rise can be attributed to an influx of migrants from countries with a higher incidence of TB. In Germany in 1993, for example, so-called 'imported' TB accounted for 2,200 new cases, People in their thirties show the highest rate, which may be up to 7 times that in the indigenous population. The situation is further exacerbated by the case-finding problems encountered in immigrant communities.

Another element in this rising trend is HIV, which has become the biggest risk factor for TB. Only one in 10 immunocompetent people infected with *M. tuberculosis*

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will fall sick in their lifetimes, but among those with HIV, 1 in 10 will develop active TB in the year of HIV infection, while 1 in 2–3 tuberculin-positive AIDS patients will succumb to the illness. In industrialized countries this is a tragedy for the individuals concerned but epidemiologically irrelevant. In the third and fourth worlds, however, the impact of HIV infection on the tuberculosis situation, especially among young adults, is truly worrying [35].

A third factor contributing to the current upswing is the emergence of multidrug resistance.

While wealthy nations with well-functioning health care systems can reasonably expect to keep TB under control, elsewhere a catastrophe looms. It is absolutely imperative that support be given to research projects devoted to improving the diagnosis of TB, speeding up resistance testing, developing effective TB immunization, and designing two or three new highly effective anti-TB drugs. Otherwise, in the long term, we are once more likely to lose our grip on 'the white plague'.

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