History of Tuberculosis. Part 1 - Phthisis, consumption and the White Plague

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> "A phthitic soldier is to his roommates what a glandered horse is to its stablemates." (Jean Antoine Villemin, French Army surgeon, 1865)[1]

Introduction

Tuberculosis is an infection with *Mycobacterium tuberculosis* which can occur in any organ of the body but is most well known in the lung. It has been a scourge throughout known history and may have killed more persons than any other microbial pathogen.[2] Paleopathological evidence dates back to 8000 BCE and evidence of bony tuberculosis has been found dating from the Neolithic period in 5800 BCE and in Egyptian mummies dating to 2400 BCE.[1, 3]

Tuberculosis was also known as *phthisis* and *consumption* from Hippocrates through to the 18th century[1], *the white death*[4] and *the great white plague*[5] during the 19th century, and other names which evoked the despair and horror of the disease such as *the robber of youth*[6], the *Captain of all these men of Death*[7], the *graveyard cough*[8], and the *King's-Evill*[4]. During the 18th and 19th centuries tuberculosis was epidemic in Europe and caused millions of deaths, particularly in the poorer classes of society. Tuberculosis declined after the late 19th century but remained a major public health issue as it still is today.[9]

Tuberculosis is an important disease for the military. During both World War I and World War II in the US Army, tuberculosis was the leading cause of discharge.[10] Annual incidence of tuberculosis in the military of Western countries is very low, however in the last several decades microepidemics have occurred in small close knit units on US and British Naval warships and land based units deployed overseas. Living and working in close quarters and overseas deployment to tuberculosis-endemic areas of the world such as Afghanistan, Iraq and South-East Asia remain significant risk factors for tuberculosis infection in military personnel, particularly multidrug resistant tuberculosis.[11, 12]

Descriptions of tuberculosis from antiquity

The legal text written in cuneiform on a stone pillar by Hammurabi, a Babylonian king, in the 2nd millennium BCE mentions a chronic lung disease which may have been tuberculosis, and a "wasting disease" was described in one of the earliest medical works, the Chinese *Huang Ti Nei-Ching* in the third millennium BCE. Homer's epic poem *Odyssey* from the 8th century BCE refers to "grievous consumption which took the soul from the body and caused a person to "lie in sickness .... a long time wasting away"".[1, 9, 13]

Hippocrates in *Book 1, Of the Epidemics* (410-400 BCE) described a disease of "weakness of the lung" with fever and cough which he refers to as *phthisis* (Gr. *phthiein* = to waste away). Phthisis was described as the commonest disease of the period and usually as being fatal.[1, 14]

> "Early in the beginning of spring, and through the summer, and towards winter, many of those who had been long gradually declining, took to bed with symptoms of phthisis; .... Many, and, in fact, most of them died, and of those confined to bed, I do not know of a single individual survived for any considerable time, ... Consumption was the most considerable of the diseases which then prevailed, and the only one which proved fatal to many persons. Most of them were affected by these diseases in the following manner; fevers accompanied with rigors, ... constant sweats, ... extremities very cold, and warmed with difficulty; bowels disordered, with bilious, scanty, unmixed, thin, pungent, and frequent dejections. The urine was thin, colourless, unconcocted, or thick, with a deficient sediment. Sputa small, dense, concocted, but brought up rarely and with difficulty; and in those who encountered the most violent symptoms there was no concoction at all, but they continued throughout spitting crude matters."[14]

Hippocrates recognised the predilection of the disease for young adults, "Phthisis makes its attacks chiefly between the age of eighteen and thirty five".[14] He also considered that pulmonary phthisis was a hereditary disease rather than an infectious one as it so commonly occurred throughout a whole family.[1,15]

Aretaeus of Cappadocia in the 2nd century CE in his work *De causis et signis diuturnorum morborum* described phthisis with wasting, coughing of blood and the formation of empyema[1, 4, 16] and wrote:

> "If from an abscess in the lung or a settled cough or spitting of blood, pus should develop within and the patient should spit it out, the disease is called *pyë* and *phthisis*. But if the chest or a rib suppurates and pus comes out through the lungs it is called *empyë*. If after this, the lung, consumed by the passage of the pus, has an abscess, it is called *phthoë*."[16]

Claudius Galen of Pergamum, a Greek physician to the Roman Emperor Marcus Aurelius in 174 CE, described phthisis with fever, sweating and coughing of blood stained sputum, and found tubercles in phthitic lungs that he called *phûma*. He considered it to be infectious and warned against close contact with people with the disease.[9, 16]

Early historical treatments

In the Hippocrates' era patients were nursed in temples and treated with plentiful and good food, milk, particularly asses' milk (it was thought asses were not prone to phthisis), and exercise. Galen and other physicians of his time recommended fresh air, milk, particularly human breast milk, eating wolf livers, drinking elephant urine, and sea voyages to regions with gentle favourable winds such as Egypt and Libya. Bloodletting was often done as it was for many diseases.[1, 2, 8, 9, 16] Aretaeus of Cappadocia recommended those "weak in the lungs" have a prolonged sojourn in the blessed cypress groves at Apollo's temple in Aquinum in Aratolia where the Sun God himself would heal them.[4] Pliny the Elder (23-79 CE) mentioned inhalation of stringent smoke and licking the limestone from Assos on the Troad coast; Pedacius Dioscorides, a Greek army surgeon in the service of Nero (54-68 CE) who wrote *Materia Medica*, recommended "warming drugs" such as animal fats; and Tertullian (160-225 CE) recommended butter boiled with honey.[16, 17]

Renaissance to the 19th century

In 1679 Sylvius de la Boë, an Amsterdam physician, in his work *Opera Medica*, was probably the first to use the term tubercles in phthisis of the lung which he called *tubercula glandulosa*, "glandulous tubercles", and described their progression to abscesses, ulcers, and empyema. In addition, Sylvius described the association between phthisis and a disease of the lymph glands of the neck called *scrofula*.[1, 13, 18]

Richard Morton, an English physician and physician to King James II, in his 1689 work *Phthisiologia* described the pathology of pulmonary and other forms of phthisis, tubercles of the lung, and scrofula. Both Sylvius and Morton considered phthisis was hereditary but Morton also considered it may be transmissible by intimate contact.[1,18] Morton described the severity of the disease in young people, "the Consumption of Young Men, that are in the Flower of their Age".[18]

In 1690 John Bunyan, British author of *Pilgrim's Progress*, in his work *The Life and Death of Mr. Badman* referred to consumption as *the Captain of all these men of Death*:

> "He parts from his wife – diseases attack him under captain consumption, he rots away, and dies in sinful security … Yet the captain of all these men of death that came against him to take him away, was the consumption, for it was that that brought him down to the grave."[7]

In 1702 Jean-Jacques Manget, a Genevan physician, observed at a post-mortem multiple small phthitic nodules in the lungs and organs which resembled millet seeds, later called "miliary tuberculosis".[1,5] In 1793 Matthew Baille, a Scottish pathologist who himself died from tuberculosis, described the caseous ("cheese-like") appearance of phthitic abscesses.[4] In 1803 Gaspard-Laurent Bayle of Vernet described the tubercle and its association with pulmonary and other forms of phthisis which he published in his 1810 work *Reserches sur la phthisie pulmonaire*.[17,18]

The term *consumption* was used as a lay term for phthisis in the 17th and 18th centuries, and both terms were used until the mid-19th century when the term tuberculosis was coined by Johann Lukas Schönlein and later used by Hermann Brehmer, Jean Antoine Villemin and Robert Koch.[1,15]

René Théophile Hyacinthe Laennec

René Théophile Hyacinthe Laennec (1781-1826) was a renowned French physician and medical researcher. He began his medical studies in Nantes, and then later at the École Pratique in Paris where he studied cadaver dissection in Guillame Dupuytrens' laboratory. Laennec distinguished himself as a

student, winning prizes in both medicine and surgery in 1801, and in 1802 he published his first paper on rheumatic fever and mitral stenosis. Later he served as editor of the *Journal de Médecine*. Laennec became known for his description of the tawny yellow nodules of micronodular cirrhosis of the liver (from Gr "kirrhos" = tawny yellow), now known as Laennec's cirrhosis.[19, 20]

In 1816 Laennec invented the stethoscope while working at the L'hôpital Necker in Paris, initially by rolling up his notebook, then later by constructing a hollow wooden cylinder.[4,19,20]

> "I therefore took a paper notebook, rolled it up tightly, applied one end to the pericardiac region and listened at the other. I was surprised as I was pleased to hear the heart beat much more clearly and distinctly."[4]

Laennec originally called his invention *le Cylindre*, but later called it a stethoscope, and called his auscultation method *l'auscultation médiate* ("mediate auscultation" - hearing carefully with the aided ear), or *stethoscopy*. Using a stethoscope helped preserve the modesty of female patients rather than having to have one's ear on the patient's chest or breast. Laennec's stethoscope was a revolutionary advance in clinical medicine enabling for the first time an accurate description of normal function and in diseases of the heart and lungs. In 1818 he presented his findings and research on stethoscopy of the chest to the *Académie des sciences* in Paris and in 1819 published them in his work *De l'auscultation mediate ou Traité du Diagnostic des Maladies des Poumon et du Coeur* (On Mediate Auscultation or Treatise on the Diagnosis of the Diseases of the Lungs and Heart).[15,19 20]

Laennec wrote an accurate and reliable description of many diseases of the chest such as bronchiectasis, pneumonia, pleurisy, and emphysema, as well as tuberculosis. He used his stethoscope to listen to the chests of tuberculous patients, identifying the presence of consolidation, pleurisy, and pulmonary cavitation. Correlating his patient examination with his dissection findings, Laennec described pulmonary and extra-pulmonary tubercles in detail and showed that they were the first phase of phthisis. He described how they first appeared in the lung in their "miliary" ("millet seed-like") form, progressing to larger tubercles containing "cheese-like" ("caseous") material, their breakdown into pus, and eventually forming cavities and empyema. He also described extra-pulmonary phthitic tubercles in the intestines, liver, meninges and other organs, and tuberculous infection in vertebrae which caused vertebral collapse and spinal cord paralysis that had been described by Sir Percivall Pott, a British surgeon, in 1779, known as Pott's disease. [4,15,17,19,20]

Laennec examined his patients according to the four pillars of French clinical method - inspection, palpation, percussion, and auscultation. He was a skilled dissector, relating findings at post-mortem to the patient's symptoms in life, and was hailed as "the greatest of teachers on tuberculosis".[4,9,17,19] He was the originator of the terms "auscultation" ("listening carefully"), "rhonchus" (a "whistling" or "snoring" sound), "pectoriloquy" ("the chest speaks"), "egophony" ("resonance"), and "râle" (a "rattling" sound) of which there were five types including "crépitation" (a "moist rattling"). Laennec died from tuberculosis in 1826.[19,20,21]

Scrofula – "the King's-Evill"

Scrofula is tuberculosis of the lymph glands of the neck with eventual ulceration and suppuration. Aristotle (384-322 BCE) and Cassius Felix (447 CE) were probably the first to describe scrofula.[1,22] Scrofula was also known in the 17th century as "*the King's-Evill*" because it was believed it could be cured by the King's touch. Richard Wiseman, who served as a ship's surgeon for the Dutch navy and later as a surgeon for King Charles' I army, wrote on the King's evil and its cure by the King in 1672 in his *Treatise of the King's-Evill* in the fourth book of his *Chirurgical Treatises*. It was not known then however that scrofula was related to phthisis or consumption.[18]

The belief that disease could be cured by a king's touch has its origins with Clovis of France (487-511), and later other European monarchs such as Robert the Pious, Edward the Confessor and Philip I of France.[17,22,23] The cure of scrofula by the King's touch was common after the 13th century and performed by English and French monarchs such as King Charles II, who during his 25 year reign touched 92,102 subjects.[4,9] Shakespeare in Macbeth, Act IV, Scene 3, refers to King Edward curing a "wretched crew of souls" of scrofula:

> " … strangely-visited people,
>
> All swoln and ulcerous, pitiful to the eye,
>
> The mere despair of surgery, he cures;
>
> Hanging a golden stamp about their necks,
>
> Put on with holy prayers.; and 'tis spoken,
>
> To the succeeding royalty he leaves
>
> The healing benediction … "[5]

Sylvius de la Boë, Richard Morton and René Laennec had all recognised that scrofula often occurred in

association with pulmonary phthisis, however the fact the two diseases had the one cause was not known until the 19th century.[1]

The epidemic of the 18th and 19th centuries and the romantic image of tuberculosis

By Laennec's era, tuberculosis had become epidemic in Europe where annual mortality rates were between 800 and 1,000 per 100,000 per year.[2] Between 1851 and 1910 in England and Wales four million died from tuberculosis, more than one third of those aged 15 to 34 and half of those aged 20 to 24 died[9], and tuberculosis was called *the robber of youth*.[6]

In that time it also became known as the great *white plague* and *the white death*[4,5,24], called "white" because of the extreme anaemic pallor of those affected.[4,25] The term *white plague* was used by Oliver Wendall Holmes, an American physician and writer, in 1861 in comparing the enormity of the epidemic to other severe plagues of the time.[26] Dormandy (1999) states that the term "white" may also have referred to its association with youth, innocence and even holiness.[4] Consumptive patients took on the appearance of a thin, pale, melancholy, almost delicate spirit. The wan and pallid facies of the victim was thought to be attractive and Dormandy states it gave women a "terrible beauty".[4]

The disease became romanticised in society by poets such as John Keats, Percy Bysshe Shelley, and George Lord Byron, and writers such as Edgar Allan Poe, Robert Louis Stevenson and Emily Brontë, many of whom themselves died from the disease.[2,4,27,28] Byrne (2011) refers to the romantic poetry of Keats and Shelley which "sought to find beauty in the horror and melancholy of consumption". Such poetry of the time was sometimes called "graveyard poetry". Byron once remarked to his friend, Lord Sligo, "I should like, I think, to die of consumption." When Lord Sligo asked why, Byron replied, "Because then all the women would say 'See that poor Byron - how interesting he looks in dying.'"[28]

John Keats wrote in 1819, "Youth grows pale, and spectre thin, and dies."[27] Keats died from tuberculosis in 1821 aged only 26 years. On a winter evening in 1818 when Keats was returning to his home in Hampstead Heath from London, he felt ill and immediately went to bed. He suddenly coughed blood onto his pillow and said to his friend John Arbuthnot Brown,

> " I know the colour of that blood. It is arterial blood, I cannot be deceived by its colour. It is my death warrant. I must die."[4, 5]

Edgar Allan Poe described his young wife, Virginia, who had tuberculosis as being 'delicately, morbidly angelic'. In 1842 while they were having dinner, Virginia had a sudden coughing fit and haemoptysis and Poe remarked :

> "Suddenly she stopped, clutched her throat and a wave of crimson blood ran down her breast ... It rendered her even more ethereal."[27]

Emily Brontë described the tuberculous heroine in *Wuthering Heights* as "rather thin, but young and fresh complexioned and her eyes sparkled like diamonds". Emily, her four sisters, and her brother Branwell died in young adulthood from tuberculosis, and their mother also died of tuberculosis.[2,4]

The imagery of the consumptive was also used by the writers of popular fiction of the 19th century who began the literary tradition of vampirism to describe vampires and their victims. Consequently it was sometimes thought, especially in areas of the world where such folklore abound such as New England in America and Yorkshire in northern Britain, that people seen to be suffering from what were actually symptoms of tuberculosis, the wasting and extreme pallor, were victims of vampires or were vampires themselves.[28]

There were certain social conditions that were intimately associated with the disease, linked to the industrial revolution at the time - poverty, malnutrition, and overcrowding. Conditions for the working classes were extremely poor.[8] In 1838 and 1839 in England between a quarter and a third of tradesmen and labourers died from tuberculosis compared to a sixth of "gentlemen".[5]

> "The disease picked out and killed a few Princes and it carried off more than one bejewelled, tender-hearted courtesan; but it slaughtered the poor by the million."[4]

Wealthy tuberculosis sufferers could afford to travel in search of sunny and mild climates or seek refuge in mountain sanatoria, whereas poorer people had to look after their own ill consumptive family in dark, unventilated, closed rooms, sealing their own fate to die of the same disease a few years later.[4,27]

The 19th century debate about the pathology and transmission of phthisis

From the beginning of the 19th century physicians debated in earnest two important questions about the pathological foundations of phthisis - firstly whether it was infectious, hereditary, or cancer, and secondly, whether scrofula, tubercles, and phthisis

were separate disease entities or manifestations of the one disease.

The most prominent proponents of a single entity were René Laennec and the Viennese pathologist Carl von Rokitansky. In contrast, Giovanna Battista Morgagni of Padua, and German physicians Rudolf Virchov and Johann Lukas Schönlein believed the diseases were separate entities.[1,3] This question wasn't settled until Robert Koch discovered in 1882 the *Tubercle bacillus* and that it was responsible for all forms of the disease.

By the 18th century many Italian physicians had come to believe that phthisis was infectious, although many British and American physicians at the time did not, and avoided doing autopsies on patients who had died from phthisis to protect themselves and their students.[1,3,5,29] Many others however still thought phthisis to be hereditary or due to constitutional weakness.[2,3] Another school of thought was that phthisis was related to *zymes*, chemicals that themselves did not cause diseases but acted as catalysts in causing decay within the body and could cause *zymotic fevers*.[9]

The 19th century saw several major breakthroughs in tuberculosis research that elucidated the infectious nature of the disease culminating in Robert Koch's discovery of the bacteria. In 1843 Philipp Friedrich Hermann Klencke, a German physician, successfully inoculated rabbits with material from a tubercle although he believed the disease to be cancer. In 1844 Friedrich Gustav Jakob Henle, a German pathologist, postulated that phthisis was infectious.[1,29]

The first breakthrough was in 1865 by Jean Antoine Villemin, a French military surgeon at the Army Medical School at Val-de Grâce. Villemin had observed that soldiers stationed for long times in barracks were more likely to have phthisis than soldiers in the field, and healthy army recruits from the country often became consumptive within a year or two of taking up their posts. He showed by controlled experiments that phthisis from humans, or tuberculosis as he also called it in his work *Cause et nature de la tuberculose: son inoculation de l'homme au lapin*, could be transmitted to rabbits demonstrating that the disease was infectious. Villemin thought that phthisis was similar to glanders, an infectious disease in horses.[1,2,4,5,17]

Koch's discovery in 1882 of the bacillus that caused tuberculosis provided more evidence that the disease was infectious. In his acceptance of his Nobel Prize in 1905 he alluded to the work of his colleague and a fellow bacteriologist, Carl Flügge, that bacilli in droplets from a cough could possibly transmit infection. However it wasn't until the mid-20th century that it was conclusively shown that tuberculosis was transmitted by the inhalation of contaminated air droplets.[30]

The term "tuberculosis"

Johann Lukas Schönlein, a German physician, in 1834 used the term tuberculosis in describing disease with tubercles, but did not use the term in relation to scrofula or phthisis.[1,5,15] In 1853 Hermann Brehmer, a medical graduate of the University of Berlin, used the term *tuberculosis of the lungs* in his doctoral thesis titled *De legibus ad initium atque progressum tuberculosis pulmonum spectantibus,* "On the Laws concerning the Beginning and Progress of Tuberculosis of the Lungs", in which he also referred to tuberculosis being curable in its early stages.[29,31] It appears that after this time the term tuberculosis supplanted phthisis, although consumption still remained as the lay term for the disease. Villemin used the term *tuberculose* in 1865 and in 1882 Robert Koch used the term *tuberkulose*, translated to English as *tuberculosis*, describing his discovery of the bacterium he called *Tubercle bacillus*, after which the disease was known as either tuberculosis or TB.[1,3,15,32]

Robert Koch's discovery paved the way for the development of the Pirquet and Mantoux tuberculin skin tests, Albert Calmette and Camille Guérin's BCG vaccine, Selman Waksman's streptomycin and other anti-tuberculous drugs. Tuberculosis is still a major public health problem today, in 2011, 8.7 million people were infected with tuberculosis with 1.4 million deaths, and mortality from tuberculosis has increased in recent decades with the emergence of HIV and of multi-drug resistant tuberculosis.

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