A little history of tuberculosis

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Introduction

It may be paradoxical to begin an account of history at the end but in the case of tuberculosis, the sequencing of the genome for *M. tuberculosis*, completed in 1998 at the Sange Institute in Paris, must rank as one of the most important developments in the study of the history of tuberculosis. There are two principal reasons for this. First it enabled scientists to confirm that human remains from prehistoric times, which were believed to show signs of tuberculous disease on clinical grounds, could now be proved to have the tubercle bacillus present in the tissues. The DNA of the bacillus could be extracted from such specimens and provide positive identification. Secondly, the structure of the genomic sequence disproved an earlier hypothesis that humans had derived their disease from the animals they kept. For this to be true, the bacteria usually causing disease in animals, *M. bovis*, would have to have been the antecedent of the human tuberculosis bacterium, *M. tuberculosis*. In fact by comparing the two bacterial genomes it is apparent that *M. tuberculosis* was, if anything, the antecedent of *M. bovis*, not the other way round. Therefore it is possible that humans gave their disease to the animals. But further study is needed on this new genome driven hypothesis.

The bacillus

The tubercle bacillus which causes the disease tuberculosis is an unusual bacterium. Its most unique property is the thick waxy outer coat it develops as “protection.” It is the Sherman tank of bacteria. From this property derives the distinctive reaction to the bacteria by the human host defenses

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which is almost entirely cell mediated. This contributes to the two distinctive forms of disease that tuberculosis causes to the human; the primary and post primary.

**The human disease**

Tubercle bacteria are transmitted by the airborne route (coughs and sneezes) from an infectious individual to another. The initial infection in the lung is a combination of local inflammation at the site of infection and enlargement of the draining lymph nodes: the so called primary complex. This process is usually sub-clinical, that is no symptoms are experienced. In about 90% of cases healing usually takes place and there are no further sequelae. The only result is that the tuberculin skin test converts from negative to positive. Sometimes the initial point of inflammation in the lung calcifies to form a spot large enough to be seen on a plain chest radiograph. Some bacilli probably remain alive and present a potential source of disease but only about one in ten individuals in this state ever go on to develop active disease.

This state is known as latent tuberculosis infection (LTBI) and approximately one third of the world population, 2 billion of us, rest happily in this position. However disease may arise in one of two ways, directly from the primary infection or after many years in the latent state by reactivation.

Disease may take a number of forms: collapse of one or more lobes of the lung, fluid forming between the lung and chest wall, disseminated or miliary disease, and the most common which is post primary lung disease resulting in slow destruction of lung tissue. In half of all cases, eventual death results if the patient is left untreated. Bacteria may also pass to other parts of the body such as the bones and joints, the lymph nodes of the neck, the brain and meninges or the genito-urinary system. This may result in extra-pulmonary disease; that is disease outside the lungs. As infection can occur at any time and the latent period last indefinitely, disease may occur at any age and in any part of the body. For those studying the history of tuberculosis, the human remains which last longest after death, and where TB can be detected most readily, are the bones of the skeleton.
Skeletal remains

We know that about 50% of skeletal tuberculosis occurs in the spine and usually shows a characteristic deformity with collapse of the body of the vertebrae causing forward angulation. In the living human the result would have been severe deformity often in the upper spine and sometimes paralysis below the point affected. Thus skeletons showing such deformities are highly likely to have been affected by tuberculosis. Genome sequencing has effectively proved that to be true. Such diseased remains have been found in humans dating back to about 5,000 B.C.

Depictions in art

A second line of evidence suggesting that tuberculosis was affecting humans at a given time is in possible depictions of disease in art. There are many such depictions, from early Egyptian art up to the present day. Some of the most moving depictions are in the pre-Raphaelite tradition of Victorian art. The patient, usually a young woman, is depicted in pale ethereal beauty with the family clustered round in despair and the attendant physician with an air of resignation by the bedside. The plague of tuberculosis has been shown to affect the human race from the beginnings of artistic history.

Written documents

A third vital contribution to our knowledge of the history of tuberculosis is through written records. Some of the earliest with any reliability were the London Bills of Mortality which listed deaths in the capital by diagnostic category. These are available from the early 17th century and show tuberculosis, or phthises as it was known then, to be amongst the more common causes of death. Of course the accuracy of diagnosis of tuberculosis at that time could not be guaranteed and many cases were probably wrongly classified.

From the early 19th century, records from the Registrar General’s statistics were available giving reasonably accurate data on the progress of disease in England and Wales. These show a steady decline in tuberculosis
deaths from about 1840. This decline continued at approximately 1.7% a year, with the exception of the periods during the two World Wars, until chemotherapy became available in the early 1950s when the decline accelerated due to the availability of specific treatment. This decline is usually attributed to the improvement in real earnings over the same period. However, we have shown that from 1840 to 1910 there was no statistically significant improvement in overall mortality or mortality from other diseases which might have been expected to be poverty related such as diphtheria and cholera. Why should tuberculosis alone show steady improvement over the same period? Could natural selection play a part?¹

*Tuberculosis and the arts*

Celebrities who have suffered and died from tuberculosis during pre-treatment times include musicians (Henry Purcell, Niccolo Paganini, Frederic Chopin, Edvard Grieg), writers (Voltaire, Walter Scott, Emily and Anne Brontë, Robert Louis Stevenson, Anton Chekhov, George Orwell), and poets (John Keats, Elizabeth Barrett Browning). Tuberculosis seems to have claimed more than its fair share of novelists, composers, artists and poets and it is tempting to suppose that the disease may have enhanced the creative instinct.

*The modern pandemic and the spread of tuberculosis*

In the early 1800s tuberculosis was the biggest killer in Western Europe. As a result of the new force of industrialization new cities were being developed which resulted in appalling housing conditions as people were thrown together in squalor and malnutrition. These would have been ideal circumstances for the spread of tuberculosis. It killed the three Brontë sisters together with one in four of the population of England. This coincided with the unique development of Britain as a world power. It was a time of the movement from Britain of armies, traders and merchants and

with them they took their infections including tuberculosis. The modern pandemic of tuberculosis which swept across the world over the next 150 years was effectively a Western European, particularly a British, export. In 1958 Grigg published a seminal paper\(^2\) in which he depicted tuberculosis as a wave of infection causing disease rates approaching 1,000 per 100,000 persons a year declining over 150 years to less than 5 per 100,000, a pattern that fits well with data from the white population of the UK over the period 1800 to 2000.

**The diagnosis of tuberculosis**

Until 1882 the cause of tuberculosis remained a mystery. There was no shortage of hypotheses. It was thought to be due to bad air by some. Others espoused a belief that it must be inherited as it tended to occur in family households. As it was closely associated with poverty and the poor tended to be despised by some, “Poor character” or “Weak personality” was considered to be a factor, not to mention bad habits or hygiene. Fortunately further speculation came to an end with Koch’s announcement on the 24 March 1882 that he had identified the bacillus which caused the disease and gave it the name *Mycobacteria tuberculosis* after the small white tubercles it was known to cause at the site of disease. The identification was further refined by Ziehl and Neelsen, two German microbiologists who gave their name to the stain used to colour the bacteria on a microscope slide, and medium was developed for its culture by Lowenstein and Jensen. Diagnosis could now depend on identifying the organism by first examining a microscope slide smeared with a specimen of sputum from the patient and then culture by incubation would confirm the identity of the organism. Though a huge step forward, these methods of diagnosis remain in place 100 years later and are relatively insensitive. The smear test detects only about half of all pulmonary cases and the culture test about 80%. A substantial number of patients are still treated on the basis of symptoms, cough, malaise, weight loss and night sweats alone, or on these together with a chest radiograph which though often showing characteristic

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abnormalities is not a specific way of confirming tuberculosis.

**A vaccine for tuberculosis: BCG**

In 1908, two Frenchmen, Calmette and Guerin, began to develop a vaccine for tuberculosis by passaging *M. bovis* 230 times. By 1921 they believed they had developed a vaccine of sufficient attenuation to provide a safe protection. A disaster occurred in Lubeck in 1927 when many children were mistakenly vaccinated with an active strain resulting in nearly one hundred deaths. Trials were halted for some time but after World War II the battle was again joined and many trials undertaken. It is not generally appreciated that about half of these trials showed no protective effect and even at its most effective BCG was shown to protect only four out of five. It seemed to give its best protection to infants against disseminated and meningeal disease. The trial carried out in Britain showed that when given to teenage children it protected three out of four for up to fifteen years. When used in this way it therefore provides some protection but is no means a guarantee against disease. Unlike the vaccine for smallpox, BCG is not effective enough to eliminate tuberculosis. New vaccines are desperately needed.

**The treatment of tuberculosis**

The first specific treatment intervention for tuberculosis was the introduction of sanatoria in the mid 1800s. A regime of bed rest followed by graded exercise, fresh air and sunlight exposure was believed to provide some hope of cure. For those who could not afford the costs, tuberculosis nurse visitors doing home visits attempted to provide advice on disease curtailment, such a getting the affected patient to sleep in a separate room from the rest of the family if this were possible.

In 1944 the first specific anti-tuberculosis drug safe enough to be used in humans was discovered in America: streptomycin. It was first introduced in trials in the UK carried out by the newly formed British Medical Research Council (BMRC). After initial success, acquired resistance which developed as a result of the bacteria being subjected to a single drug, lead to many disappointments. By good fortune a second
specific drug was being developed in Europe: para-amino salicylic acid (PAS). When used in combination with streptomycin cure of over 90% of patients could be achieved but best results were only obtained if treatment was continued for two years. A few years later the most effective drug at killing the tubercle bacillus was developed: isoniazid. When the three drugs were combined treatment time could be reduced to eighteen months. At last the tuberculosis sanatoria were emptying.

Over the next two decades further anti-tuberculosis drugs were discovered which could be added to the treatment regimen. Some, such as pyrazinamide, caused unacceptable side effects in the dosage used and fell out of favor for a time. Others, such as ethambutol, though not particularly effective in killing bacteria, were useful in combination with other drugs in preventing the emergence of resistance.

In the late 1960s a new, and perhaps the most important, drug in the treatment of tuberculosis was discovered: Rifampicin. This drug was able to kill the very slowly dividing bacteria, the so-called "persisters" which the other drugs could not. It was found that by combining this drug with at least two others initially, the length of treatment time could be reduced to as little as six months. So the new standard of treatment of tuberculosis became isoniazid (H), rifampicin (R), and pyrazinamide (Z) for two months followed by isoniazid and rifampicin for four months. This is conveniently abbreviated to 2HRZ/4HR.

A study directed by Wallace Fox of the BMRC and carried out by the Tuberculosis Research Centre in Madras, India, showed that home treatment of tuberculosis was just as successful as hospital treatment. This meant that the great expense of hospitalization could largely be avoided, a very important saving in resource poor countries.

Unfortunately the very success of the drug treatment of tuberculosis has been the catalyst for the emergence of a new wave of drug resistance. Patients have been allowed to take their medication at home in a completely unsupervised way. The experience of the early single use of streptomycin taught us that taking one drug on its own for tuberculosis would lead to drug resistance.

Using the specialist tuberculosis nurse visitors in a new role as treatment supervisors, the UK had been fortunate in avoiding the numbers of drug resistant cases but poor medical practice and patient co-operation
has resulted in a slight increase. Across the world it remains a very great concern.

**The current picture of tuberculosis**

Despite all these advances, tuberculosis is currently increasing across the world at about 1% a year. Population growth, HIV, which renders the human body uniquely susceptible to tuberculosis, and poverty are causing a rapid increase in some parts of the developing world, particularly Sub-Saharan Africa. It is estimated that each year 10 million new cases of tuberculosis occur, of which 2 million die. In 1993 the WHO declared tuberculosis to be a global emergency and advocated DOTS (directly observed therapy) as a means of control. This method relies on governmental co-operation, good quality drugs, good recording of patient monitoring and results, first class microscopy for diagnosis and, above all, observation of the patient as they take their medication.

**The future**

The need for new drugs, vaccines and diagnostic methods for tuberculosis is obvious. To finish at the beginning it can only be hoped that the sequencing of the bacterial genome will provide these tools in the battle against tuberculosis. If they do not we are in serious danger of losing the war against this resurgent disease.

**Further reading**
