Mycobacterium tuberculosis has been present in the human population since antiquity - fragments of the spinal column from Egyptian mummies from 2400 B.C. show definite pathological signs of tubercular decay.

The term phthisis, consumption, appears first in Greek literature. Around 460 B.C., Hippocrates identified phthisis as the most widespread disease of the times, and noted that it was almost always fatal. Due to common phthisis related fatalities, he wrote something no doctor would dare write today: he warned his colleagues against visiting cases in late stages of the disease, because their inevitable deaths might damage the reputations of the attending physicians.

Exact pathological and anatomical descriptions of the disease began to appear in the seventeenth century. In his *Opera Medica* of 1679, Sylvius was the first to identify actual tubercles as a consistent and characteristic change in the lungs and other areas of consumptive patients. He also described their progression to abscesses and cavities. Manget described the pathological features of miliary tuberculosis in 1702. The earliest references to the infectious nature of the disease appear in seventeenth century Italian medical literature. An edict issued by the Republic of Lucca in 1699 states that, "henceforth, human health should no longer be endangered by objects remaining after the death of a consumptive. The names of the deceased should be reported to the authorities, and measures undertaken for disinfection."

In 1720, the English physician Benjamin Marten was the first to conjecture, in his publication, *A New Theory of Consumption*, that TB could be caused by "wonderfully minute living creatures", which, once they had gained a foothold in the body, could generate the lesions and symptoms of the disease. He stated, moreover, "It may be therefore very likely that by an habitual lying in the same bed with a consumptive patient, constantly eating and drinking with him, or by very frequently conversing so nearly as to draw in part of the breath he emits from the Lungs, a consumption may be caught by a sound person...I imagine that slightly conversing with consumptive patients is seldom or never sufficient to catch the disease." For the early eighteenth century, Dr. Marten's writings display a great degree of epidemiological insight.

In contrast to this significant level of understanding about the etiology of consumption, which was already enabling prevention and a break in the chain of infection, those attempting to cure the disease were still groping in the dark

The introduction of the sanatorium cure provided the first really step against TB. Hermann Brehmer, a Silesian botany student suffering from TB, was instructed by his doctor to seek out a healthier climate. He traveled to the Himalayan mountains where he could pursue his botanical studies while trying to rid himself of the disease. He returned home cured and began to study medicine. In 1854, he presented his doctoral dissertation bearing the auspicious title, *Tuberculosis is a Curable Disease*>. In the same year, he built an institution in Gorbersdorf where, in the midst of fir trees, and with good nutrition, patients were exposed on their balconies to continuous fresh air. This setup became the

blueprint for the subsequent development of sanatoria, a powerful weapon in the battle against an insidious opponent.

New advances then followed in rapid succession. In 1865, the French military doctor Jean-Antoine Villemin single-handily demonstrated that consumption could be passed from humans to cattle and from cattle to rabbits. On the basis of this revolutionary evidence, he postulated a specific microorganism as the cause of the disease, finally laying to rest the centuries-old belief that consumption arose spontaneously in each affected organism.

In 1882, Robert Koch discovered a staining technique that enabled him to see *Mycobacterium tuberculosis*. What excited the world was not so much the scientific brilliance of Koch's discovery, but the accompanying certainty that now the fight against humanity's deadliest enemy could really begin.

The measures available to doctors were still modest. Improving social and sanitary conditions, and ensuring adequate nutrition were all that could be done to strengthen the body's defenses against the TB bacillus. Sanatoria, now to be found throughout Europe and the United States, provided a dual function: they isolated the sick, the source of infection, from the general population, while the enforced rest, together with a proper diet and the well-regulated hospital life assisted the healing processes.

These efforts were reinforced by the observation of the Italian Forlanini, that lung collapse tended to have a favorable impact on the outcome of the disease. With the introduction of artificial pneumothorax and surgical methods to reduce the lung volume, the depressing era of helplessness in the face of advanced TB was over, and active therapy had begun.

A further significant advance came in 1895 when Wilhelm Konrad von Rontgen discovered the radiation that bears his name. Now the progress and severity of a patient's disease could be accurately followed and reviewed.

Another important development was provided by the French bacteriologist Calmette, who, together with Guerin, used specific culture media to lower the virulence of the bovine TB bacterium, creating the basis for the BCG vaccine still in widespread use today. Then, in the middle of World War II, came the final breakthrough, the greatest challenge to the bacterium that had threatened humanity for thousands of years - chemotherapy.

In fact, the chemotherapy of infectious diseases, using sulfonamide and penicillin, had been underway for several years, but these molecules were ineffective against *Mycobacterium tuberculosis*. Since 1914, Selman A. Waksman had been systematically screening soil bacteria and fungi, and at the University of California in 1939 had discovered the marked inhibitory effect of certain fungi, especially actinomycete, on bacterial growth. In 1940, he and his team were able to isolate an effective anti-TB

antibiotic, actinomycin; however, this proved to be too toxic for use in humans or animals.

Success came in 1943. In test animals, streptomycin, purified from *Streptomyces griseus*, combined maximal inhibition of *M. tuberculosis* with relatively low toxicity. On November 20, 1944, the antibiotic was administered for the first time to a critically ill TB patient. The effect was almost immediately impressive. His advanced disease was visibly arrested, the bacteria disappeared from his sputum, and he made a rapid recovery. The new drug had side effects - especially on the inner ear - but the fact remained, *M. tuberculosis* was no longer a bacteriological exception, it could be assailed and beaten into retreat within the human body.

A rapid succession of anti-TB drugs appeared in the following years. These were important because with streptomycin monotherapy, resistant mutants began to appear with a few months, endangering the success of antibiotic therapy. However, it was soon demonstrated that this problem could be overcome with the combination of two or three drugs.

Chemotherapy Today

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 *B*-lactam antibiotic with a *B*-lactamase inhibitor enhance treatment effectiveness, but the newer drugs, including the macrolides, have not received much clinical testing.

Two properties of anti-TB drugs are important: antibacterial activity, highest in

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isoniazid
rifampin
streptomycin

and their capacity to inhibit the development of resistance, the most effective drugs being

isoniazid
rifampin
ethambutol

With the proper four drug regimen, there should be a rapid clinical improvement and a significant fall in the bacterial count. After a month, the patient should be afebrile, feel well and have regained weight. Coughing and sputum should have diminished and improvements will be visible on the X-rays.

Although bacteria will still be present in the smears, they will become more and more difficult to culture. Improvements will be visible on the X-rays for three to four months. If the disease was initially severe, though, the end of treatment may not be reached for a year.

The absence of radiological improvement in the first three months should be grounds for concern and indicate that a change in therapy is needed. Patient compliance and the bacteria's drug sensitivity should be reevaluated. Relapses usually occur within six months of the end of treatment, and in most cases are due to poor patient compliance. Patient compliance must be monitored throughout treatment; this is done at the National Tuberculosis Center through

Directly observed therapy

When TB becomes active again in a previously treated patient, there is a high chance that the bacteria will now be drug resistant. Any current therapy must be suspended until multiple drugs are found to which the pathogen is fully sensitive, and treatment can be resumed with the addition of these drugs to the original regimen. Never add a single drug to a failing regimen. If the microorganism is resistant to the standard drugs, then it will be necessary to administer more toxic medications such as

ethionamide
pyrazinamide
cycloserine
capreomycin
viomycin
kanamycin

The Recent TB Epidemic

The registered number of new cases of TB worldwide roughly correlates with economic conditions: the highest incidences are seen in those countries of Africa, Asia, and Latin America with the lowest gross national products. WHO estimates that eight million people get TB every year, of whom 95% live in developing countries. An estimated 3 million people die from TB every year.

In industrialized countries, the steady drop in TB incidence began to level off in the mid 1980s and then stagnated or even began to increase. Much of this rise can be at least partially attributed to a high rate of immigration from countries with a high incidence of TB. It is also difficult to perform epidemiological surveillance and treatment in immigrant communities due to various cultural differences.

A great influence in the rising TB trend is HIV infection. Chances are that only one out of ten immunocompetent people infected with *M. tuberculosis* will fall sick in their lifetimes, but among those with HIV, one in ten per year will develop active TB, while one in two or three tuberculin test positive AIDS patients will develop active TB. In many industrialized countries this is a tragedy for the patients involved, but it these cases make up only a small minority of TB cases. In developing countries, the impact of HIV infection on the TB situation, especially in the 20-35 age group, is worthy of concern.

A final factor contributing to the resurgence of TB is the emergence of multi-drug resistance. Drug resistance in TB occurs as a result of tubercle bacillus mutations. These mutations are not dependent upon the presence of the drug. Exposed to a single effective anti-TB medication, the predominant bacilli, sensitive to that drug, are killed; the few drug resistant mutants, likely to be present if the bacterial population is large, will, multiply freely. Since it is very unlikely that a single bacillus will spontaneously mutate to resistance to more than one drug, giving multiple effective drugs simultaneously will inhibit the multiplication of these resistant mutants. This is why it is absolutely essential to treat TB patients with the recommended four drug regimen of isoniazid, rifampin, pyrazinamide and ethambutol or streptomycin.

While wealthy industrialized countries with good public health care systems can be expected to keep TB under control, in much of the developing world a catastrophe awaits. It is crucially important that support be given to research efforts devoted to developing an effective TB vaccine, shortening the amount of time required to ascertain drug sensitivities, improving the diagnosis of TB, and creating new, highly effective anti-TB medications. Without support for such efforts, we run the risk of losing the battle against TB.

Written by John Tranotti