

# TUBERCULOSIS

- Scourge of the human species

## INTRODUCTION:

Tuberculosis (TB) is an age-old disease known to civilization since pre-historic times. It is caused by bacterial infection. Although it can affect many parts of the human body, the most commonly found disease affects the lungs. In earlier times, TB was called "Consumption" or "White Plague" and it was a major killer. Even now, TB remains one of the most common infectious diseases known to man. Nearly 32 per cent of the human population (nearly 1.9 billion people) is infected with the TB pathogen. Approximately 9 million of these infected people develop active disease and more than two million of these patients die from the disease each year. **In India alone one person dies of TB every minute.**

## THE PATHOGEN:

TB is caused by bacteria that belong to a class of micro-organisms called *Mycobacteria*. The species of bacteria that most commonly infect humans is called *Mycobacterium tuberculosis*. There are also other species, which infect other animals (e.g., cattle, *Mycobacterium bovis*; birds, *Mycobacterium avium*) but rarely infect humans. Another related group of bacteria, *Mycobacterium leprae*, causes leprosy.

*Mycobacteria* are long, rod shaped cells that develop into long chains (bacillae), which look like a string of sausages when stained and seen under a microscope. Their cell walls contain a special lipid substance called mycolic acid that is found only in *Mycobacteria*. The presence of mycolic acid makes the cells water-repelling (hydrophobic) - an effect similar to oil on water. This property is important because normal staining procedures used for other bacteria cannot be used for staining *Mycobacteria*. Microbiologists use a special procedure called acid-fast staining to make *Mycobacteria* visible under the microscope.

*Mycobacterium tuberculosis* can be grown in the laboratory, but growth is very slow: laboratory confirmation of an infection may take 2-3 weeks. Sometimes culturing may fail, although the disease can still often be diagnosed from various other clinical symptoms

## TRANSMISSION OF TUBERCULOSIS:

When people breath out, yawn, speak, sing, or sneeze, air containing millions of tiny water droplets come out of their mouth. These droplets (also called an aerosol), too small to be seen, remain floating in the air, and may be breathed in by other people nearby. In people infected with TB, this aerosol may contain the TB bacteria, thereby spreading the infection from one person to another. TB is most commonly spread from a person with untreated disease to other people sharing the same living and/or working space.

## DEVELOPMENT OF PULMONARY TB:

Aerosol inhalation of TB bacteria may infect a person with healthy lungs. However, the first infection usually heals. If the same person becomes infected again, the disease is more like take hold. If it is not discovered (diagnosed) early, the disease spreads within the lung. Here it forms holes (cavities), the numbers of which

increase as the disease progresses, ultimately leading to the destruction of the entire lung. The most common symptoms indicating that the disease has become established in the lungs are persistent coughing, producing a viscous secretion called sputum, and having a fever for more than a week. Acid-fast staining of a smear of this sputum usually reveals the presence of TB bacteria. In its early stages the disease often remains unnoticed.

TB infection typically goes through three stages in humans:

1. **"Early Infection"**, which often heals without being noticed.
2. **"Dormant TB"**, **"Latent TB"** or **"Sleeping TB"**, which occurs when TB bacteria remain in the body in a dormant state, without any apparent ill-effect on the health of the individual. In many cases this stage may last for years, or even decades.
3. The dormant infection "wakes up" and causes the disease as described earlier. This stage is referred to as **"Active TB"**.

### **EXTRA-PULMONARY TUBERCULOSIS:**

The TB bacteria may affect almost any part of the body. The lungs are the most common site of infection, and other parts of the body are more susceptible to the disease than others. These are; the bones and joints, the lymphatic, reproductive, urinary and digestive systems.

The TB bacteria reach the lungs by aerosol inhalation, where they multiply. They then move to the lymph nodes at the root of the lung. These will normally control the bacteria, but some may escape this control system, overwhelming the lymph nodes in the chest and spreading throughout the body via the lymphatic channels and blood vessels. If large numbers of TB bacteria escape suddenly into the blood stream, the disease develops rapidly and affects many other organs. This condition is called *"generalized miliary tuberculosis"*. This is a serious condition which often leads to **Tuberculous meningitis**. Tubercular meningitis, the most serious form of the disease, is very dangerous. Headache, stiffness of the neck and fever give early warning, delirium, coma and death follow if TB meningitis remains untreated.

The TB bacteria can also reach the bones and joints by way of the blood stream, as the body's resistance mechanisms fail to stop them. In such cases the pathogenic bacteria often attack the spine, and less often the hip, knee, foot, and ankle. When the knee is affected, the disease spreads and inflames the lining of the joint. Fluid collects and destruction of the bone begins. The patient suffers pain, swelling and stiffness, forcing a limp and if they remain untreated permanent deformity and crippling will result. As the disease progresses, abscesses also appear.

The kidney is another important organ that may be invaded by TB bacteria from the blood stream. In this case, the disease develops very slowly, and years may elapse before symptoms appear. These are frequent urination, pus and blood in the urine, unexplained fever and loss of weight.

The reproductive system in both males and females is also affected by the invasion of the TB bacteria. Fallopian and uterine tubes are often the targets of the disease in women, while in men, the prostate gland is the most susceptible organ.

TB rarely appears in the stomach, gall bladder or the pancreas, but it may occur in the intestines or the rectum. Less often, the liver is affected.

In the new millennium, TB is posing a greater global problem than in the twentieth century. The disease continues to kill young and middle aged adults faster than any

other disease and its association with the Acquired Immune Deficiency Syndrome (AIDS) is causing a greater threat to humanity than ever before.

## **DIAGNOSIS:**

TB cases are either infectious (pulmonary, sputum-smear positive) or non-infectious (pulmonary but sputum-smear negative or extrapulmonary). Acid-fast stained bacteria in sputum smear from cases of suspected TB, observed under the microscope, are found mainly in those patients with relatively advanced pulmonary TB. Microbiological culturing of TB bacteria is a difficult, time-consuming laboratory technique, which requires the expertise of trained clinical microbiologists.

Another commonly employed test is called the Mantoux or tuberculin skin test. A tiny amount of protein, extracted from the bacteria, is injected into the skin. If the subject is currently infected, or has ever been infected with the bacteria, a positive test results. In 24 hours or so, a hard, red nodule develops at the site of the injection. The test indicates the presence of infection by TB bacteria, although it does not necessarily mean the person has TB. A positive result may also be caused by BCG vaccination, or by infection with other non-TB bacteria.

There are no simple, reliable tests currently available for TB, although recent progress in research may lead to the development of new diagnostic procedures that are accurate, fast and easy to perform.

## **TREATMENT:**

Vaccination with BCG (Bacillus Calmette Guérin) has not proved effective in reducing the incidence of TB, particularly in India. Drug treatment has proved to be effective, but it requires the oral administration of four drugs (isoniazid, ethambutol, rifampicin and pyrazinamide) for between three or six months and a year. Such long courses inevitably lead to people forgetting to take their medicine, which, in turn, leads to the emergence of bacteria resistant to antibiotics. This has resulted in the recent introduction of shorter courses of treatment lasting for two months, where a healthcare professional actually supervises the patient taking their medication (Directly Observed Treatment Shortcourse (DOTS)). However, the problem of TB bacteria resistant to a number of antibiotics (Multiple Drug Resistant (MDR)) is still growing.

### **The Need for New anti-TB Drugs**

Global Alliance for TB Drug Development has recommended that a new treatment should offer at least one of the following three improvements over existing ones:

- Shorten the total duration of effective treatment and/or significantly reduce the total number of doses needed to be taken under DOTS
- Improve the treatment of MDR-TB, which cannot be treated with isoniazid and rifampicin
- Provide a more effective treatment of latent TB infection.

## **ASTRAZENECA'S COMMITMENT TO COMBATING TUBERCULOSIS**

**Research Centre of Excellence, Bangalore, India**

In August 2000, AstraZeneca announced the establishment of a Research Centre of Excellence in Bangalore, India, to focus on the discovery of new treatments for tuberculosis (TB) and other diseases found primarily in the developing world.

This US \$35 million initiative is part of AstraZeneca's commitment to the development of novel therapies to treat infectious diseases that pose an increased threat to developing nations. AstraZeneca is the only pharmaceutical company in the world with a research programme in India totally dedicated to TB.

The Bangalore Research Centre of Excellence currently houses more than 60 scientists recruited from leading research institutions across the world, and plans to recruit more international experts over the next five years.

The medicines now used to treat TB were developed more than forty years ago: since that time there has been limited progress in developing new therapies against this increasing global health threat. The lack of new treatments has been compounded by the increasing ability of infectious organisms to evolve, adapt and develop resistance to existing drug therapies.

AstraZeneca scientists in Bangalore, in collaboration with AstraZeneca genomics and infection research centres in Boston, USA, and Cheshire, UK, are employing advanced techniques to develop improved diagnostic tests, identify new treatment targets and uncover more effective therapies against the disease that overcome the increasing problem of drug resistance.

Early detection of those with TB through correct diagnosis could prevent the disease from being passed on, and could stop a wrongly diagnosed patient from receiving costly and inappropriate medicines for the condition's treatment period of six months.

The ability to eradicate TB infection from the body is a pre-requisite for an ideal anti-tubercular medicine. Efforts are therefore focussing on understanding the mechanism by which the TB microbe evades both the immune system and current treatments. They are also concentrating on identifying people at particular risk of TB infection, as only 30 per cent of people exposed to TB become infected.

## **AstraZeneca**

AstraZeneca is one of the five leading pharmaceutical companies in the world. The company's interests include therapeutic areas such as Oncology, Gastrointestinal, Cardiovascular, Respiratory, Central Nervous System, Pain Control and Infection.

AstraZeneca completely owns AstraZeneca India (Private) Limited, a Research & Development unit focusing on the discovery of novel therapeutics for infectious diseases of the developing world such as TB.