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TUBERCULOSIS - AN OVERVIEW

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ABSTRACT

Tuberculosis remains the most important communicable disease in the world. The World Health organization (WHO) estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis.* Groups that are at high risk for tuberculosis infection include HIV-infected persons, immigrants from countries with high rates of tuberculosis, the homeless, health care professionals, intravenous drug users, persons taking immunosuppressive agents, and those in institutional settings, such as nursing homes and correctional facilities. Along with the recent increase in cases of tuberculosis, there is a progressive increase in multidrug resistant (MDR) tuberculosis. Some of the MDR isolates are resistant to as many as seven of the commonly employed antimycobacterial drugs.

Key words: Multidrug resistant (MDR), *M. Tuberculosis,*Granuloma, MODS assay and Paracas-Caverna culture.

INTRODUCTION, HISTORY AND BACKGROUND

Tuberculosis (TB) is an infection, primarily in the lungs (a pneumonia), caused by bacteria called *Mycobacterium tuberculosis*. It was first isolated in 1882 by a German physician named *Robert Koch* who received the Nobel Prize for this discovery. TB most commonly affects the lungs but also can involve almost any organ of the body. Many years ago, this disease was referred to as "*consumption" because* without effective treatment, these patients often would waste away. Today, of course, tuberculosis usually can be treated successfully with antibiotics.

Tubercular decay has been found in the spines of Egyptian mummies. Pictured: Egyptian mummy in the British Museum. Tuberculosis has been present in humans since antiquity. The earliest unambiguous detection of *Mycobacterium tuberculosis* is in the remains of bison dated 18,000 years before the present [1]. Whether tuberculosis originated in cattle and then transferred to humans, or diverged from a common ancestor infecting a different species, is currently unclear [2]. However, it is clear that *M. tuberculosis* is not directly descended from *M. bovis*, which seems to have evolved relatively recently [3].

Skeletal remains from a Neolithic Settlement in the Eastern Mediterranean show prehistoric humans (7000 BC) had TB [4], and tubercular decay has been found in the spines of mummies from 3000–2400 BC [5]. Phthisis is a Greek term for tuberculosis; around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times involving coughing up blood and fever, which was almost always fatal [6]. In South America, the earliest evidence of tuberculosis is associated with the Paracas-Caverna culture (circa 750 BC to circa 100 AD) [7,8]. Skeletal remains from prehistoric North America indicate that the disease was so common that "virtually every member of these late prehistoric communities had primary exposure to tuberculosis [9].

CAUSES

The cause of TB, *Mycobacterium tuberculosis* (MTB), is a small aerobic non-motile bacillus. High lipid content of this pathogen accounts for many of its unique clinical characteristics [10]. It divides every 16 to 20 hours, an extremely slow rate compared with other bacteria, which usually divide in less than an hour [11]. (For example, one of the fastest-growing bacteria is a strain of *E. coli* that can

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divide roughly every 20 minutes.) Since MTB has a cell wall but lacks a phospholipid outer membrane, it is classified as a Gram-positive bacterium. However, if a Gram stain is performed, MTB either stains very weakly Gram-positive or does not retain dye due to the high lipid & mycolic acid content of its cell wall [12]. MTB can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured *in vitro* [13].

Using histological stains on expectorate samples from phlegm (also called sputum), scientists can identify MTB under a regular microscope. Since MTB retains certain stains after being treated with acidic solution, it is classified as an acid-fast bacillus (AFB) [14,12]. The most common acid-fast staining technique, the Ziehl-Neelsen stain, dyes AFBs a bright red that stands out clearly against a blue background. Other ways to visualize AFBs include an auramine-rhodamine stain and fluorescent microscopy.

The *M. tuberculosis* complex includes four other TB-causing mycobacteria: *M. bovis*, *M. africanum*, *M. canetti* and *M. microti* [15]. *M. africanum* is not widespread, but in parts of Africa it is a significant cause of tuberculosis [16,17]. *M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurized milk has largely eliminated this as a public health problem in developed countries [14,18]. *M. canetti* is rare and seems to be limited to Africa, although a few cases have been seen in African emigrants [19]. *M. microti* is mostly seen in immunodeficient people, although it is possible that the prevalence of this pathogen has been underestimated [20].

Other known pathogenic mycobacteria include *Mycobacterium leprae*, *Mycobacterium marinum*, *Mycobacterium avium* and *M. kansasii*. The last two are part of the nontuberculous mycobacteria (NTM) group. Nontuberculous mycobacteria cause neither TB nor leprosy, but they *do* cause pulmonary diseases resembling TB [21].

RISK FACTORS

Persons with silicosis have an approximately *30-fold* greater risk for developing TB [22]. Silica particles irritate the respiratory system, causing immunogenic responses such as phagocytosis, which, as a consequence, results in high lymphatic vessel deposits [23]. It is this interference and blockage of macrophage function that increases the risk of tuberculosis [24]. Persons with chronic renal failure and also on hemodialysis have an increased risk: 10–26 times greater than the general population. Persons with diabetes mellitus have a risk for developing active TB that is two to four times greater than persons without diabetes mellitus, and this risk is likely greater in persons with insulin-dependent or poorly controlled diabetes. Other clinical conditions that have been associated with active TB include gastrectomy with attendant weight loss and malabsorption, jejunoileal bypass, renal and cardiac transplantation, carcinoma of the head or neck, and other neoplasms (e.g., lung cancer, lymphoma, and leukemia) [25].

Given that silicosis greatly increases the risk of tuberculosis, more research about the effect of various indoor or outdoor air pollutants on the disease would be necessary. Some possible indoor sources of silica include paint, concrete and Portland cement. Crystalline silica is found in concrete, masonry, sandstone, rock, paint, and other abrasives. The cutting, breaking, crushing, drilling, grinding, or abrasive blasting of these materials may produce fine silica dust. It can also be in soil, mortar, plaster, and shingles. When you wear dusty clothing at home or in your car, you may be carrying silica dust that your family will breathe [26].

Low body weight is associated with risk of tuberculosis as well. A body mass index (BMI) below 18.5 increases the risk by 2—3 times. On the other hand, an increase in body weight lowers the risk [27,28]. Patients with diabetes mellitus are at increased risk of contracting tuberculosis [29], and they have a poorer response to treatment, possibly due to poorer drug absorption [30].

Other conditions that increase risk include the sharing of needles among IV drug users; recent TB infection or a history of inadequately treated TB; chest X-ray suggestive of previous TB, showing fibrotic lesions and nodules; prolonged corticosteroid therapy and other immunosuppressive therapy; Immunocompromised patients (30-40% of AIDS patients in the world also have TB) hematologic and reticuloendothelial diseases, such as leukemia and Hodgkin's disease; end-stage kidney disease; intestinal bypass; chronic malabsorption syndromes; vitamin D deficiency [31]; and low body weight [32].

Twin studies in the 1940s showed that susceptibility to TB was heritable. If one of a pair of twins got TB, then the other was more likely to get TB if he was identical than if he was not [33] These findings were more recently confirmed by a series of studies in South Africa [34,35,36]. Specific gene polymorphisms in *IL12B* have been linked to tuberculosis susceptibility [37].

Some drugs, including rheumatoid arthritis drugs that work by blocking tumor necrosis factor-alpha (an inflammation-causing cytokine), raise the risk of activating a latent infection due to the importance of this cytokine in the immune defense against TB [38].

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PATHOGENESIS

About 90% of those infected with *Mycobacterium tuberculosis* have asymptomatic, latent TB infection (sometimes called LTBI), with only a 10% lifetime chance that a latent infection will progress to TB disease. However, if untreated, the death rate for these active TB cases is more than 50%.

TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within the endosomes of alveolar macrophages. The primary site of infection in the lungs is called the Ghon focus, and is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe. Bacteria are picked up by dendritic cells, which do not allow replication, although these cells can transport the bacilli to local (mediastinal) lymph nodes. Further spread is through the bloodstream to other tissues and organs where secondary TB lesions can develop in other parts of the lung (particularly the apex of the upper lobes), peripheral lymph nodes, kidneys, brain, and bone. All parts of the body can be affected by the disease, though it rarely affects the heart, skeletal muscles, pancreas and thyroid.

Tuberculosis is classified as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding the infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes secrete cytokines such as interferon gamma, which activates macrophages to destroy the bacteria with which they are infected. Cytotoxic T cells can also directly kill infected cells, by secreting perforin and granulysin.

Importantly, bacteria are not always eliminated within the granuloma, but can become dormant, resulting in a latent infection. Another feature of the granulomas of human tuberculosis is the development of abnormal cell death, also called necrosis, in the center of tubercles. To the naked eye this has the texture of soft white cheese and was termed caseous necrosis.

If TB bacteria gain entry to the bloodstream from an area of damaged tissue they spread through the body and set up many foci of infection, all appearing as tiny white tubercles in the tissues. This severe form of TB disease is most common in infants and the elderly and is called miliary tuberculosis. Patients with this disseminated TB have a fatality rate near 100% if untreated. However, If treated early, the fatality rate is reduced to near 10%.

In many patients the infection waxes and wanes. Tissue destruction and necrosis are balanced by healing and fibrosis. Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. During active disease, some of these cavities are joined to the air passages bronchi and this material can be coughed up. It contains living bacteria and can therefore pass on infection. Treatment with appropriate antibiotics kills bacteria and allows healing to take place. Upon cure, affected areas are eventually replaced by scar tissue. If untreated, infection with *Mycobacterium tuberculosis* can become lobar pneumonia.

PROGNOSIS

Progression from TB infection to TB disease occurs when the TB bacilli overcome the immune system defenses and begin to multiply. In primary TB disease 1-5% of cases this occurs soon after infection. However, in the majority of cases, a latent infection occurs that has no obvious symptoms. These dormant bacilli can produce tuberculosis in 2-23% of these latent cases, often many years after infection. The risk of reactivation increases with immunosuppression, such as that caused by infection with HIV. In patients co-infected with *M. tuberculosis* and HIV, the risk of reactivation increases to 10% per year. Studies utilizing DNA fingerprinting of *M. tuberculosis* strains have shown that reinfection contributes more substantially to recurrent TB than previously thought, with between 12% and 77% of cases attributable to reinfection (instead of reactivation).

HOW DOES A PERSON GET TB?

A person can become infected with tuberculosis bacteria when he or she inhales minute particles of infected sputum from the air. The bacteria get into the air when someone who has a tuberculosis lung infection coughs, sneezes, shouts, or spits (which is common in some cultures). People who are nearby can then possibly breathe the bacteria into their lungs. You don't get TB by just touching the clothes or shaking the hands of someone who is infected. Tuberculosis is spread (transmitted) primarily from person to person by breathing infected air during close contact (**figure1**).

There is a form of atypical tuberculosis, however, that is transmitted by drinking unpasteurized milk. Related bacteria, called *Mycobacterium bovis*, cause this form of TB. Previously, this type of bacteria was a major cause of TB in children, but it rarely causes TB now since most milk is pasteurized (undergoes a heating process that kills the bacteria).

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WHAT HAPPENS TO THE BODY WHEN A PERSON GETS TB?

When the inhaled tuberculosis bacteria enter the lungs, they can multiply and cause a local lung infection (pneumonia). The local lymph nodes associated with the lungs may also become involved with the infection and usually become enlarged. The haler lymph nodes (the lymph nodes adjacent to the heart in the central part of the chest) are often involved (**figure 2**).

In addition, TB can spread to other parts of the body (**figure 3**). The body's immune (defense) system, however, can fight off the infection and stop the bacteria from spreading. The immune system does so ultimately by forming scar tissue around the TB bacteria and isolating it from the rest of the body. Tuberculosis that occurs after initial exposure to the bacteria is often referred to as primary TB. If the body is able to form scar tissue (fibrosis) around the TB bacteria, then the infection is contained in an inactive state. Such an individual typically has no symptoms and cannot spread TB to other people. The scar tissue and lymph nodes may eventually harden, like stone, due to the process of calcification of the scars (deposition of calcium from the bloodstream in the scar tissue). These scars often appear on X-rays and imaging studies like round marbles and are referred to as a granuloma. If these scars do not show any evidence of calcium on X-ray, they can be difficult to distinguish from cancer.

Sometimes, however, the body's immune system becomes weakened, and the TB bacteria break through the scar tissue and can cause active disease, referred to as reactivation tuberculosis or secondary TB. For example, the immune system can be weakened by old age, the development of another infection or a cancer, or certain medications such as cortisone, anticancer drugs, or certain medications used to treat arthritis or inflammatory bowel disease. The breakthrough of bacteria can result in a recurrence of the pneumonia and a spread of TB to other locations in the body. The kidneys, bone, and lining of the brain and spinal cord (meninges) are the most common sites affected by the spread of TB beyond the lungs.

HOW COMMON IS TB AND WHO GETS IT?

Over 8 million new cases of TB occur each year worldwide. In the United States, it is estimated that 10-15 million people are infected with the TB bacteria and 22,000 new cases of TB occur each year.

Anyone can get TB, but certain people are at higher risk, including

- People who live with individuals who have an active TB infection,
- Poor or homeless people,
- Foreign-born people from countries that have a high prevalence of TB,
- Nursing-home residents and prison inmates,
- Alcoholics and intravenous drug users,
- People with diabetes, certain cancers, and HIV infection (the AIDS virus),
- Health-care workers.

There is no strong evidence for a genetically determined (inherited) susceptibility for TB.

SYMPTOMS OF TB

As previously mentioned, TB infection usually occurs initially in the upper part (lobe) of the lungs. The body's immune system, however, can stop the bacteria from continuing to reproduce. Thus, the immune system can make the lung infection inactive (dormant). On the other hand, if the body's immune system cannot contain the TB bacteria, the bacteria will reproduce (become active or reactivate) in the lungs and spread elsewhere in the body.

It may take many months from the time the infection initially gets into the lungs until symptoms develop. The usual symptoms that occur with an active TB infection are a generalized tiredness or weakness, weight loss, fever, and night sweats. If the infection in the lung worsens, then further symptoms can include coughing, chest pain, coughing up of sputum (material from the lungs) and/or blood, and shortness of breath. If the infection spreads beyond the lungs, the symptoms will depend upon the organs involved **(figure 4).**

DIAGNOSIS OF TB

TB can be diagnosed in several different ways, including chest X-rays, analysis of sputum, and skin tests. Sometimes, the chest X-rays can reveal evidence of active tuberculosis pneumonia. Other times, the X-rays may show scarring (fibrosis) or hardening (calcification) in the lungs, suggesting that the TB is contained and inactive. Examination of the sputum on a slide (smear) under the microscope can show the presence of the tuberculosis-like bacteria. Bacteria of the *Mycobacterium* family, including atypical mycobacteria, stain positive with special dyes and are referred to as acid-fast bacteria (AFB). A sample of the sputum also is usually taken and grown (cultured) in special incubators so that the tuberculosis bacteria can subsequently be identified as tuberculosis or atypical tuberculosis.

Several types of skin tests are used to screen for TB infection. These so-called tuberculin skin tests include the Tine test and the Mantoux test, also known as the PPD (purified protein derivative) test. In each of these tests, a small amount of purified extract from dead tuberculosis bacteria is injected under the skin. If a person is not infected with TB, then no reaction will occur at the site of the injection (a negative skin test). If a person

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is infected with tuberculosis, however, a raised and reddened area will occur around the site of the test injection. This reaction, a positive skin test, occurs about 48-72 hours after the injection. When only the skin test is positive, or evidence of prior TB is present on chest X-rays, the disease is referred to as "latent tuberculosis." This contrasts with active TB as described above, under symptoms.

If the infection with tuberculosis has occurred recently, however, the skin test can be falsely negative. The reason for a false-negative test with a recent infection is that it usually takes two to 10 weeks after the time of infection with tuberculosis before the skin test becomes positive. The skin test can also be falsely negative if a person's immune system is weakened or deficient due to another illness such as AIDS or cancer, or while taking medications that can suppress the immune response, such as cortisone or anticancer drugs.

Bacille Calmette Guérin, also known as BCG, is a vaccine given throughout many parts of the world. It is derived from an atypical *Mycobacterium* but offers some protection from developing active tuberculosis, especially in infants and children. This vaccination is believed to be important in parts of the world where TB is quite common. This is not the case in the United States. When BCG has been administered, future PPD and Tine skin tests remain positive and can cause some confusion when trying to diagnose TB. It is also important to realize that even with a BCG vaccine in childhood, tuberculosis can still occur in an adult exposed to the tuberculosis bacteria, which calls into question the real utility and effectiveness of this vaccination.

A new blood test is now available that can help distinguish between a prior BCG vaccine and a positive PPD due to TB infection. This test involves mixing the patient's blood with substances that produce a TB-like immune response. After a period of time, the immune cells, if infected with TB, produce interferon-gamma, a protein produced by the body to defend against an infection. This test, like most, is not perfect, but with the proper clinical information can help distinguish a real TB infection from a positive reaction on the test due to a prior BCG vaccine.

NEW DIAGNOSTIC METHODS

1.Automated culture methods: Liquid media for cultivation of mycobacteria had never attracted the attention of mycobacteriologists. In fact, the ability of a liquid medium to support a faster growth was heavily hampered by its susceptibility to contamination. The use of antimicrobial combinations suitable of inhibiting the growth of the whole spectrum of potential contaminants (Gram-positive and Gramnegative bacteria as well as fungi) represented a turning point. During the same period, automation was taking its first steps in microbiology, with blood cultures leading the field. The apparently banal idea of exporting such technology to mycobacterial cultures evolved into selective liquid media, which were breakthrough for diagnostic mycobacteriology.

2.Nucleic acid amplification methods: When the polymerase chain reaction (PCR) methodology took its first steps into diagnostic microbiology, a restricted number of micro-organisms appeared to have the potential to benefit from the novel technique. *M. tuberculosis* was among them, and the dream of the rapid diagnosis of TB appeared to be about to come true.

3.Genetic identification methods: Following the extraordinary development of molecular methods, the identification of mycobacteria, previously based on phenotypic investigations, suddenly started to rely on genotypic methods. Different genetic approaches developed in research laboratories became rapidly popular in diagnostic laboratories and some of them were transformed into commercial diagnostic kits.

- PCR restriction-enzyme analysis
- DNA probes
- Genetic sequencing

4.Non-conventional phenotypic diagnostic methods: In addition to the so-called conventional methods for TB diagnosis and besides the automated and molecular diagnostic methods described above, some new technologies have been proposed, such as phage-based assays and rapid detection of growth by microscopic observation of microcolonies in solid or liquid media. The phage-based assay relies on the ability of *M. tuberculosis* to support the growth of an infecting mycobacteriophage. The number of endogenous phages, representing the original number of viable bacilli, is then determined in a lawn of a rapidly growing mycobacterium such as *M. smegmatis* (McNerney 2001). The micro-colony method or thin-layer agar technique is an old method for culturing and identifying mycobacteria; it allows both rapid detection and presumptive identification of isolates based on the characteristic morphology of mycobacteria in culture, and has been proposed as an inexpensive alternative method for the rapid detection and culture of mycobacteria (Welch 1993). Microscopic observation broth-drug susceptibility assay (MODS) has been described for the early detection of *M. tuberculosis* growth in liquid medium, allowing a more timely diagnosis and drug susceptibility testing. The method is based on the observation of the characteristic cord formation of *M. tuberculosis* visualized microscopically in liquid medium with the use of an inverted microscope (Caviedes 2000). In this study,

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sputum samples were analyzed by staining, cultivation, and PCR. Sensitivity of MODS (92 %) compared favourably with the most sensitive of the other culture methods (93 %) with a median turnaround time of nine days. The method has been proposed as a rapid, inexpensive, sensitive, and specific method for *M. tuberculosis* detection and susceptibility testing, appropriate for use in developing countries. In a recent operational study conducted in Peru, the performance of the MODS assay was investigated for the rapid diagnosis of TB (Moore 2006). The assay was compared with an automated mycobacterial culture system and culture on Löwenstein-Jensen medium. The sensitivity for the detection of *M. tuberculosis* was 97.8 % compared to 89.0 % for the automated mycobacterial culture, and 84.0 % for Löwenstein-Jensen medium ($P < 0.001$); the median turnaround time was 7, 13, and 26 days for MODS, the automated culture system, and Löwenstein-Jensen medium, respectively ($P < 0.001$). One limitation of the MODS assay is the requirement for an inverted microscope, which is necessary to observe the cord formation in liquid medium.

KEY CONCEPTS IN THE TREATMENT OF TUBERCULOSIS

The ability of the tubercle bacillus to remain dormant but viable and capable of causing disease is a major therapeutic challenge. The mycobacteria are slow growing intracellular organisms that require the administration of a combination of drugs for extended periods to achieve effective therapy and to prevent the emergence of resistance. The risk of adverse reactions therefore must be a major consideration in drug selection. The three basic concepts in tuberculosis treatment are as follows: (1) Regimens must contain multiple drugs to which the organism is susceptible. (2) Drugs must be taken regularly. (3) Drug therapy must con-tinue for a sufficient time.Traditionally, Antitubercular drugs are the antibiotics used in prevention and treatment of tuberculosis caused by the bacteria mycobacterium tuberculosis. Some of the drugs are used to diagnosis the disease such as Isoniazid , Rifampicin, ethambutol and Pyrizanamide. They are first line drugs used for treating tuberculosis.

In short course treatment of tuberculosis the Isoniazid, Rifampicin, pyrazinamide and ethambutol is given for 2 months followed by Isoniazid and Rifampicin alone for 4 months.

Second line drugs for treatment of tuberculosis

- Aminoglycosides like Amikacin, kanamycin.
- Polypeptides like capreomycin.
- Fluoroquinolones like ciprofloxacin, levofloxacin, moxifloxacin
- Thioamides like ethionamide, prothionamide
- Cycloserine
- Para aminosalicylic acid

Third line drugs for tuberculosis

- Rifabutin
- Macrolides like clarythromycin
- Linezolid
- Thioacetazone
- Vitamin D
- Thioridazine

Use of steroids in tuberculosis

Steroids like predinisolone and dexamethasone are used in tubercular meningitis, tubercular pericarditis and tubercular peritonitis.

Adverse effects of antitubercular drugsNausea

- Vomiting
- Loss of appetite
- Itching
- Joint pains
- Burning sensation in feet
- Jaundice
- Skin rash
- Angina
- Constipation
- Seating
- Sleeplessness
- Bitter taste
- Body pain

Isoniazid (also called **isonicotinyl hydrazine** or **INH**; sold as **Laniazid**, **Nydrazid**) is an organic compound that is the first-line antituberculosis medication in prevention and treatment. First discovered in 1912 as an inhibitor of the MAO enzyme, it was first used as an antidepressant, but discontinued due to side effects. In 1951, it was later discovered that isoniazid was effective against TB. Isoniazid is never used on its own to treat active tuberculosis because resistance quickly develops. The compound was first synthesised in the early 20th century, but its activity against tuberculosis was first reported in the early 1950's and three pharmaceutical companies attempted unsuccessfully to simultaneously patent the drug.

MECHANISM OF ACTION

Isoniazid is a prodrug and must be activated by bacterial catalase. It is activated by catalase-peroxidase enzyme KatG which couples the isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to ketoenoylreductase known as InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthase.

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This process inhibits the synthesis of mycolic acid required for the mycobacterial cell wall. A range of radicals are produced by KatG activation of Isoniazid, including nitric oxide that has also been shown to be important in the action of another antimycobacterial prodrug PA824.

A person with a positive skin test, a normal chest X-ray, and no symptoms most likely has only a few TB germs in an inactive state and is not contagious. Nevertheless, treatment with an antibiotic may be recommended for this person to prevent the TB from turning into an active infection. The antibiotic used for this purpose is called isoniazid (INH). If taken for six to 12 months, it will prevent the TB from becoming active in the future. In fact, if a person with a positive skin test does not take INH, there is a 5%-10% lifelong risk that the TB will become active.

Taking isoniazid can be inadvisable (contraindicated) during pregnancy or for those suffering from alcoholism or liver disease. Also, isoniazid can have side effects. The side effects occur infrequently, but a rash can develop, and the individual can feel tired or irritable. Liver damage from isoniazid is a rare occurrence and typically reverses once the drug is stopped. Very rarely, however, especially in older people, the liver damage (INH hepatitis) can even be fatal. It is important therefore, for the doctor to monitor a patient's liver by periodically ordering blood tests called "liver function tests" during the course of INH therapy. Another side effect of INH is a decreased sensation in the extremities referred to as a peripheral neuropathy. This can be avoided by taking vitamin B6 (pyridoxine), and this is often prescribed along with INH. A person with a positive skin test along with an abnormal chest X-ray and sputum evidencing TB bacteria has active TB and is contagious. As already mentioned, active TB usually is accompanied by symptoms, such as a cough, fever, weight loss, and fatigue.

Active TB is treated with a combination of medications along with isoniazid. Rifampin (Rifadin), ethambutol (Myambutol), and pyrazinamide are the drugs commonly used to treat active TB in conjunction with isoniazid (INH). Four drugs are often taken for the first two months of therapy to help kill any potentially resistant strains of bacteria. Then the number is usually reduced to two drugs for the remainder of the treatment based on drug sensitivity testing that is usually available by this time in the course. Streptomycin, a drug that is given by injection, may be used as well, particularly when the disease is extensive and/or the patients do not take their oral medications reliably (termed "poor compliance"). Treatment usually lasts for many months and sometimes for years. Successful treatment of TB is dependent largely on the compliance of the patient. Indeed, the failure of a patient to take the medications as prescribed is the most important cause of failure to cure the TB infection. In some locations, the health department demands direct monitoring of patient compliance with therapy.

Surgery on the lungs may be indicated to help cure TB when medication has failed, but in this day and age, surgery for TB is unusual. Treatment with appropriate antibiotics will usually cure the TB. Without treatment, however, tuberculosis can be a lethal infection. Therefore, early diagnosis is important. Those individuals who have been exposed to a person with TB, or suspect that they have been, should be examined by a doctor for signs of TB and screened with a TB skin test.

PUBLIC HEALTH

Tuberculosis is one of the three primary diseases of poverty along with AIDS and malaria. The Global Fund to Fight AIDS, Tuberculosis and Malaria was started in 2002 to raise finances to address these infectious diseases. Globalization has led to increased opportunities for disease spread. A tuberculosis scare occurred in 2007 when Andrew Speaker flew on a transatlantic flight infected with multi-drug-resistant tuberculosis.
In the United States, the National Center for HIV, STD, and TB Prevention, as part of the Centers for Disease Control and Prevention (CDC), is responsible for public health surveillance and prevention research.

RESEARCH

The Mycobacterium Tuberculosis Structural Genomics Consortium is a global consortium of scientists conducting research regarding the diagnosis and treatment of tuberculosis. They are attempting to determine the 3-dimensional structures of proteins from *M. Tuberculosis*.

TUBERCULOSIS AT A GLANCE

- Tuberculosis is spread usually from person to person by breathing infected air during close contact.
- TB can remain in an inactive (dormant) state for years without causing symptoms or spreading to other people.
- When the immune system of a patient with dormant TB is weakened, the TB can become active (reactivate) and cause infection in the lungs or other parts of the body.
- The risk factors for acquiring TB include close-contact situations, alcohol and IV drug abuse, and certain diseases (for example, diabetes, cancer, and HIV) and occupations (for example, health-care workers).
- The most common symptoms of TB are fatigue, fever, weight loss, coughing, and night sweats.
- The diagnosis of TB involves skin tests, chest X-rays, sputum analysis (smear and culture), and PCR tests to detect the genetic material of the causative bacteria.

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- Inactive tuberculosis may be treated with an antibiotic, isoniazid (INH), to prevent the TB infection from becoming active.
- Active TB is treated, usually successfully, with INH in combination with one or more of several drugs, including rifampin, ethambutol, pyrazinamide, and streptomycin.
- Drug-resistant TB is a serious, as yet unsolved, public-health problem, especially in Southeast Asia, the countries of the former Soviet Union, Africa, and in prison populations. Poor patient compliance, lack of detection of resistant strains, and unavailable therapy are key reasons for the development of drug-resistant TB.
- The occurrence of HIV has been responsible for an increased frequency of tuberculosis. Control of HIV in the future, however, should substantially decrease the frequency of TB.

Figure 1: Transmission of tuberculosis

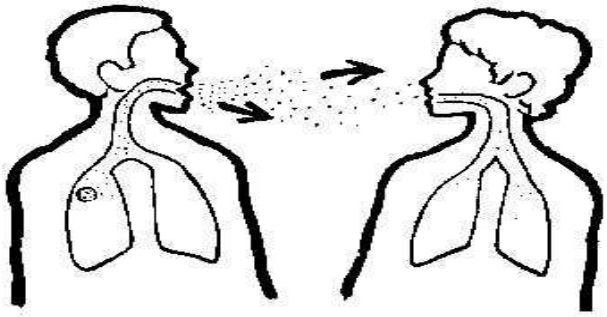


Figure 2: Association of local lymph nodes with the lungs

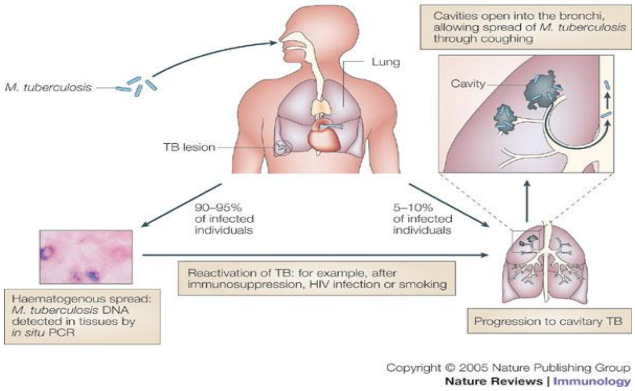


Figure 3: Spreading to all over the body

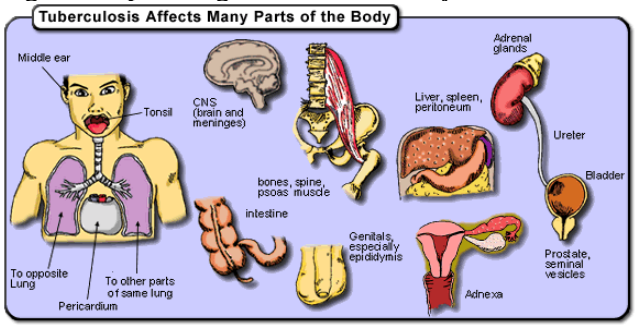
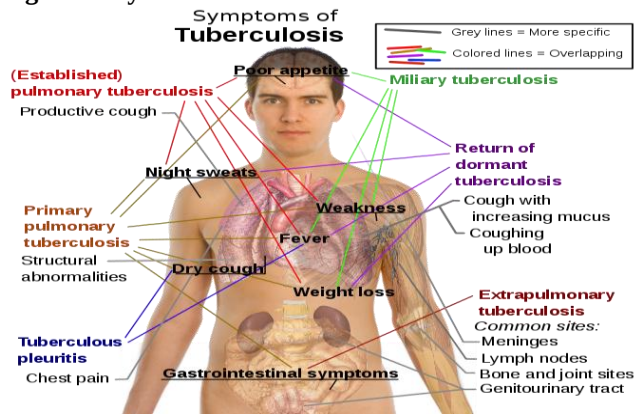


Figure 4: Symtoms of Tuberculosis



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