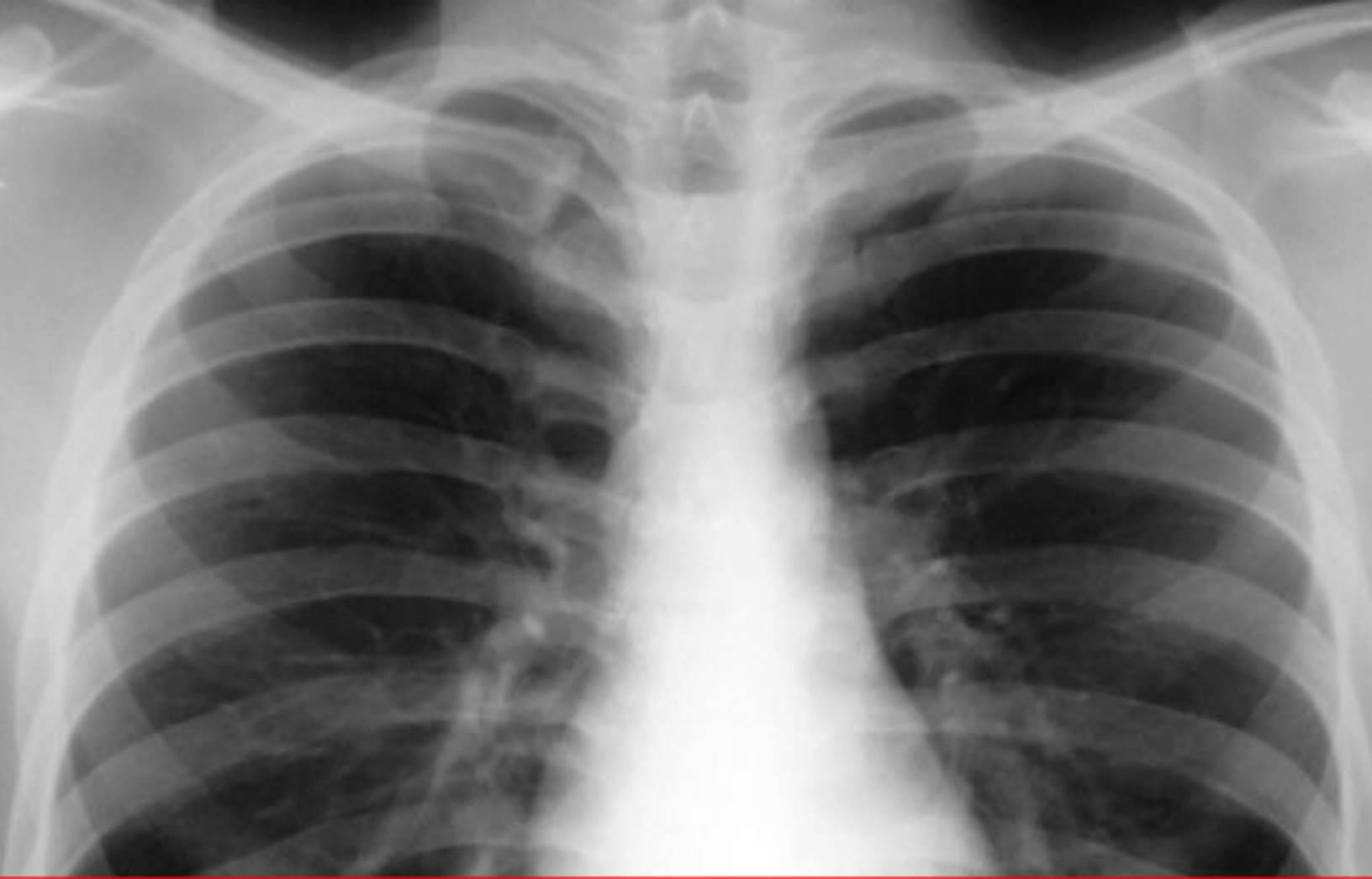

Tuberculosis and Asthma

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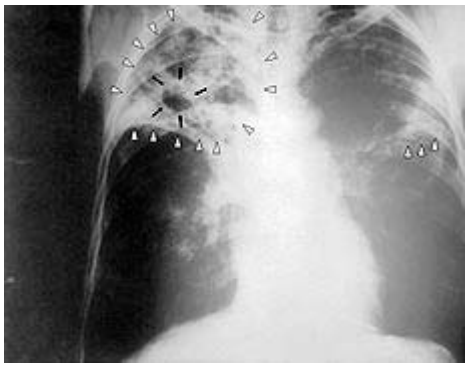
Tuberculosis

Tuberculosis



Chest X-ray of a patient with far-advanced tuberculosis

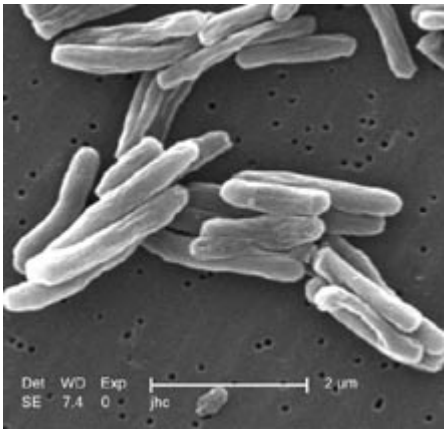
ICD-10	A15.–A19.
ICD-9	010–018
OMIM	607948
DiseasesDB	8515
MedlinePlus	000077 *000624*
eMedicine	med/2324 emerg/618 radio/411
MeSH	D014376

Tuberculosis, **MTB** or **TB** (short for *tubercles bacillus*) is a common and in some cases deadly infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* in humans. Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air when people who have active MTB infection cough, sneeze, or spit. Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of its victims.

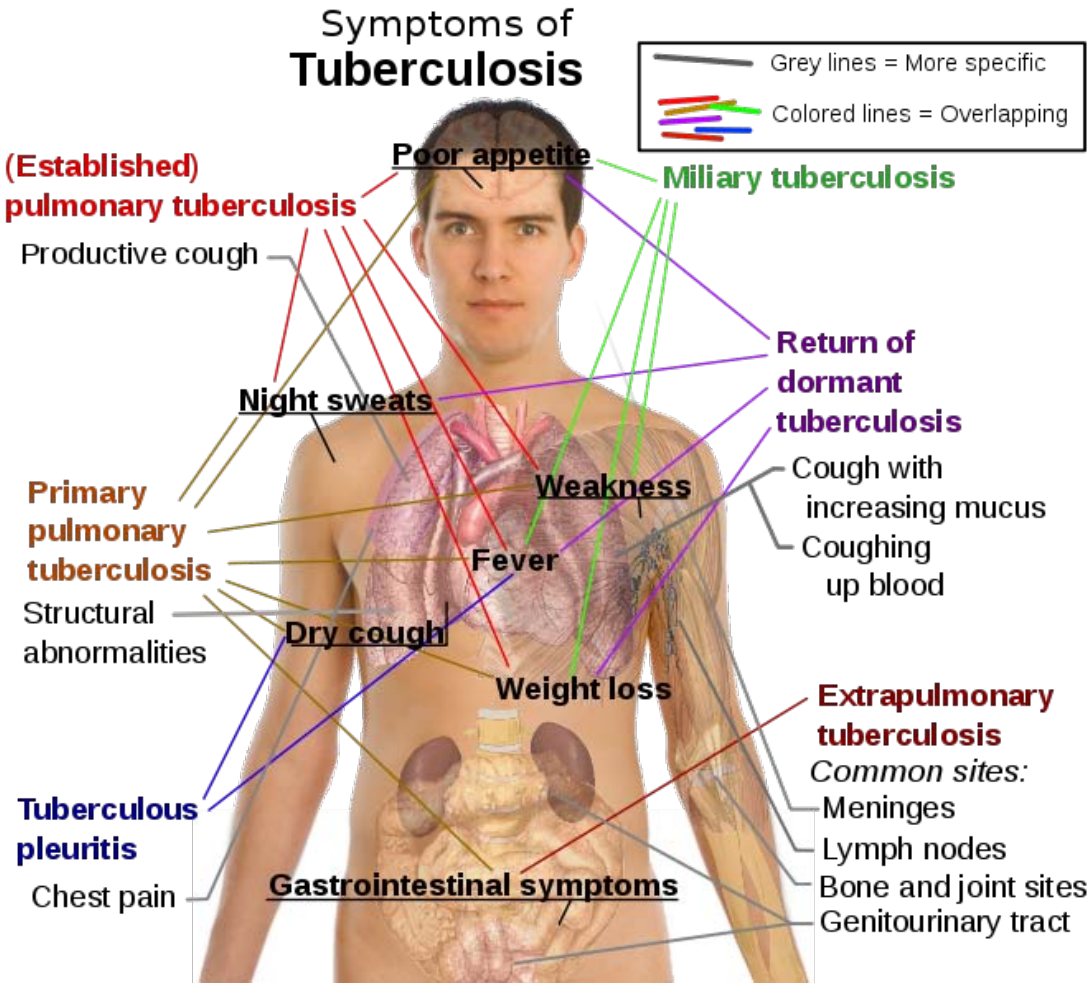
The classic symptoms are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss (the last giving rise to the formerly prevalent colloquial term "consumption"). Infection of other organs causes a wide range of symptoms. Diagnosis relies on radiology (commonly chest X-rays), a tuberculin skin test, blood tests, as well as microscopic examination and microbiological culture of bodily fluids. Treatment is difficult and requires long courses of multiple antibiotics. Contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in (extensively) multi-drug-resistant tuberculosis. Prevention relies on screening programs and vaccination, usually with Bacillus Calmette-Guérin vaccine.

One third of the world's population is thought to be infected with *M. tuberculosis*, and new infections occur at a rate of about one per second. The proportion of people who become sick with tuberculosis each year is stable or falling worldwide but, because of population growth, the absolute number of new cases is still increasing. In 2007 there were an estimated 13.7 million chronic active cases, 9.3 million new cases, and 1.8 million deaths, mostly in developing countries. In addition, more people in the developed world contract tuberculosis because their immune systems are more likely to be compromised due to higher exposure to immunosuppressive drugs, substance abuse, or AIDS. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5-10% of the US population test positive.

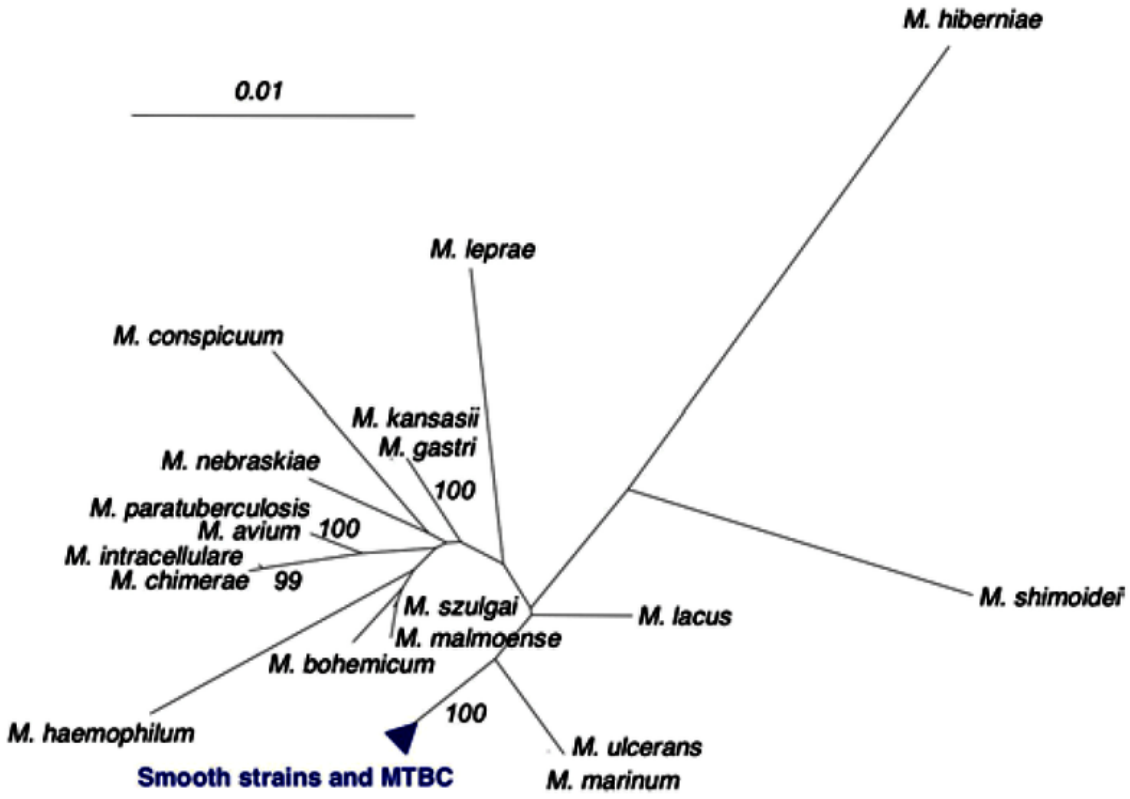
Signs and symptoms



Scanning electron micrograph of *Mycobacterium tuberculosis*



Main symptoms of variants and stages of tuberculosis, with many symptoms overlapping with other variants, while others are more (but not entirely) specific for certain variants. Multiple variants may be present simultaneously.



Phylogenetic tree of the genus *Mycobacterium*

When the disease becomes active, 75% of the cases are pulmonary TB, that is, TB in the lungs. Symptoms include chest pain, coughing up blood, and a productive, prolonged cough for more than three weeks. Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, pallor, and fatigue.

Tuberculosis also has a specific odour attached to it, this has led to trained animals being used to vet samples as a method of early detection

In the other 25% of active cases, the infection moves from the lungs, causing other kinds of TB, collectively denoted extrapulmonary tuberculosis. This occurs more commonly in immunosuppressed persons and young children. Extrapulmonary infection sites include the pleura in tuberculosis pleurisy, the central nervous system in meningitis, the lymphatic system in scrofula of the neck, the genitourinary system in urogenital tuberculosis, and bones and joints in Pott's disease of the spine. An especially serious form is disseminated TB, more commonly known as miliary tuberculosis. Extrapulmonary TB may co-exist with pulmonary TB as well.

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. It divides every 16 to 20 hours, an extremely slow rate compared with other bacteria, which usually divide in less than an hour. (For example, one of the fastest-growing bacteria is a strain of *E. coli* that can 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. 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*.

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). 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*. *M. africanum* is not widespread, but in parts of Africa it is a significant cause of tuberculosis. *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. *M. canetti* is rare and seems to be limited to Africa, although a few cases have been seen in African emigrants. *M. microti* is mostly seen in immunodeficient people, although it is possible that the prevalence of this pathogen has been underestimated.

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.

Risk factors

Persons with silicosis have an approximately *30-fold* greater risk for developing TB. Silica particles irritate the respiratory system, causing immunogenic responses such as phagocytosis, which, as a consequence, results in high lymphatic vessel deposits. It is this interference and blockage of macrophage function that increases the risk of tuberculosis. 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).

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.

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. Patients with diabetes mellitus are at increased risk of contracting tuberculosis, and they have a poorer response to treatment, possibly due to poorer drug absorption.

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; and low body weight.

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. These findings were more recently confirmed by a series of studies in South Africa. Specific gene polymorphisms in *IL12B* have been linked to tuberculosis susceptibility.

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.

Mechanism

Transmission

When people suffering from active pulmonary TB cough, sneeze, speak, or spit, they expel infectious aerosol droplets 0.5 to 5 μm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very low and inhaling fewer than ten bacteria may cause an infection.

People with prolonged, frequent, or intense contact are at particularly high risk of becoming infected, with an estimated 22% infection rate. A person with active but untreated tuberculosis can infect 10–15 other people per year. Others at risk include

people in areas where TB is common, people who inject drugs using unsanitary needles, residents and employees of high-risk congregate settings, medically under-served and low-income populations, high-risk racial or ethnic minority populations, children exposed to adults in high-risk categories, patients immunocompromised by conditions such as HIV/AIDS, people who take immunosuppressant drugs, and health care workers serving these high-risk clients.

Transmission can only occur from people with active — not latent — TB. The probability of transmission from one person to another depends upon the number of infectious droplets expelled by a carrier, the effectiveness of ventilation, the duration of exposure, and the virulence of the *M. tuberculosis* strain. The chain of transmission can, therefore, be broken by isolating patients with active disease and starting effective anti-tuberculous therapy. After two weeks of such treatment, people with non-resistant active TB generally cease to be contagious. If someone does become infected, then it will take at least 21 days, or three to four weeks, before the newly infected person can transmit the disease to others. TB can also be transmitted by eating meat infected with TB. *Mycobacterium bovis* causes TB in cattle.

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.

Diagnosis

Mycobacterium tuberculosis (stained red) in sputum

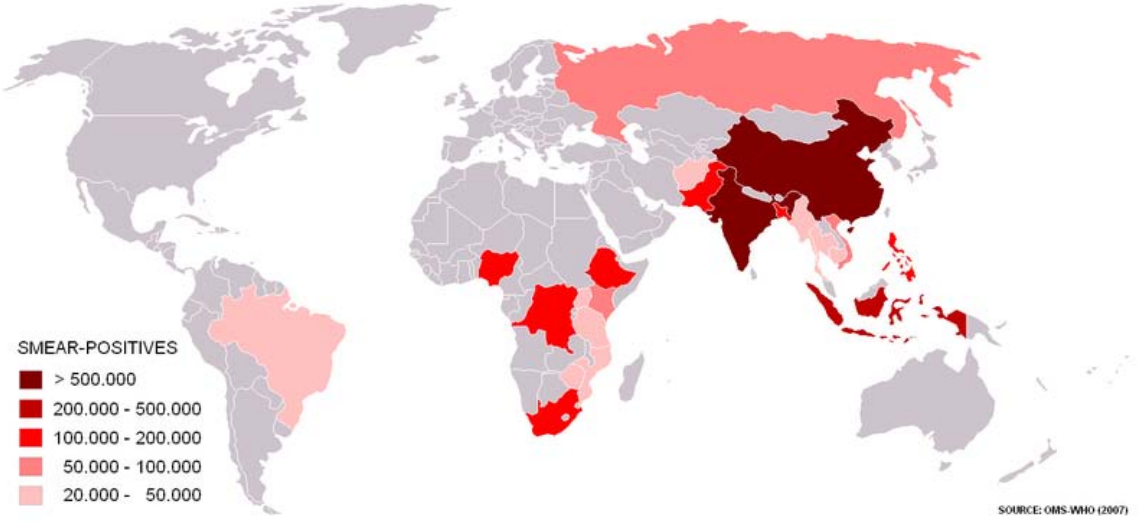
Tuberculosis is diagnosed definitively by identifying the causative organism (*Mycobacterium tuberculosis*) in a clinical sample (for example, sputum or pus). When this is not possible, a probable - although sometimes inconclusive - diagnosis may be made using imaging (X-rays or scans) and/or a tuberculin skin test (Mantoux test).

The main problem with tuberculosis diagnosis is the difficulty in culturing this slow-growing organism in the laboratory (it may take 4 to 12 weeks for blood or sputum culture). A complete medical evaluation for TB must include a medical history, a physical examination, a chest X-ray, microbiological smears, and cultures. It may also include a tuberculin skin test, a serological test. The interpretation of the tuberculin skin test depends upon the person's risk factors for infection and progression to TB disease, such as exposure to other cases of TB or immunosuppression.

Currently, latent infection is diagnosed in a non-immunized person by a tuberculin skin test, which yields a delayed hypersensitivity type response to an extract made from *M. tuberculosis*. Those immunized for TB or with past-cleared infection will respond with delayed hypersensitivity parallel to those currently in a state of infection, so the test must be used with caution, particularly with regard to persons from countries where TB immunization is common. Tuberculin tests have the disadvantage of producing false negatives, especially when the patient is co-morbid with sarcoidosis, Hodgkins lymphoma, malnutrition, or most notably active tuberculosis disease. The newer interferon release assays (IGRAs) overcome many of these problems. IGRAs are *in vitro* blood tests that are more specific than the skin test. IGRAs detect the release of interferon gamma in response to mycobacterial proteins such as ESAT-6. These are not affected by immunization or environmental mycobacteria, so generate fewer false positive results. There is also evidence that the T-SPOT.*TB* IGRA is more sensitive than the skin test.

New TB tests have been developed that are fast and accurate. These include polymerase chain reaction assays for the detection of bacterial DNA. One such molecular diagnostics text gives results in 100 minutes and is being currently offered to 116 low and middle-income countries at a discount with support from WHO and the Bill and Melinda Gates foundation.

Prevention



Map showing the 22 high-burden countries (HBC) that according to WHO account for 80% of all new TB cases arising each year. The Global Plan is especially aimed at these countries.

TB prevention and control takes two parallel approaches. In the first, people with TB and their contacts are identified and then treated. Identification of infections often involves testing high-risk groups for TB. In the second approach, children are vaccinated to protect them from TB. No vaccine is available that provides reliable protection for adults. However, in tropical areas where the levels of other species of mycobacteria are high, exposure to nontuberculous mycobacteria gives some protection against TB.

The World Health Organization (WHO) declared TB a global health emergency in 1993, and the Stop TB Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between 2006 and 2015. Since humans are the only host of *Mycobacterium tuberculosis*, eradication would be possible. This goal would be helped greatly by an effective vaccine.

Vaccines

Many countries use Bacillus Calmette-Guérin (BCG) vaccine as part of their TB control programmes, especially for infants. According to the WHO, this is the most often used vaccine worldwide, with 85% of infants in 172 countries immunized in 1993. One country that notably does not widely administer BCG is the United States, where TB is rather uncommon. BCG was the first vaccine for TB and developed at the Pasteur Institute in France between 1905 and 1921. However, mass vaccination with BCG did not start until after World War II. The protective efficacy of BCG for preventing serious forms of TB (e.g. meningitis) in children is greater than 80%; its protective efficacy for preventing pulmonary TB in adolescents and adults is variable, ranging from 0 to 80%.

In South Africa, the country with the highest prevalence of TB, BCG is given to all children under age three. However, BCG is less effective in areas where mycobacteria are less prevalent; therefore BCG is not given to the entire population in these countries. In the USA, for example, BCG vaccine is not recommended except for people who meet specific criteria:

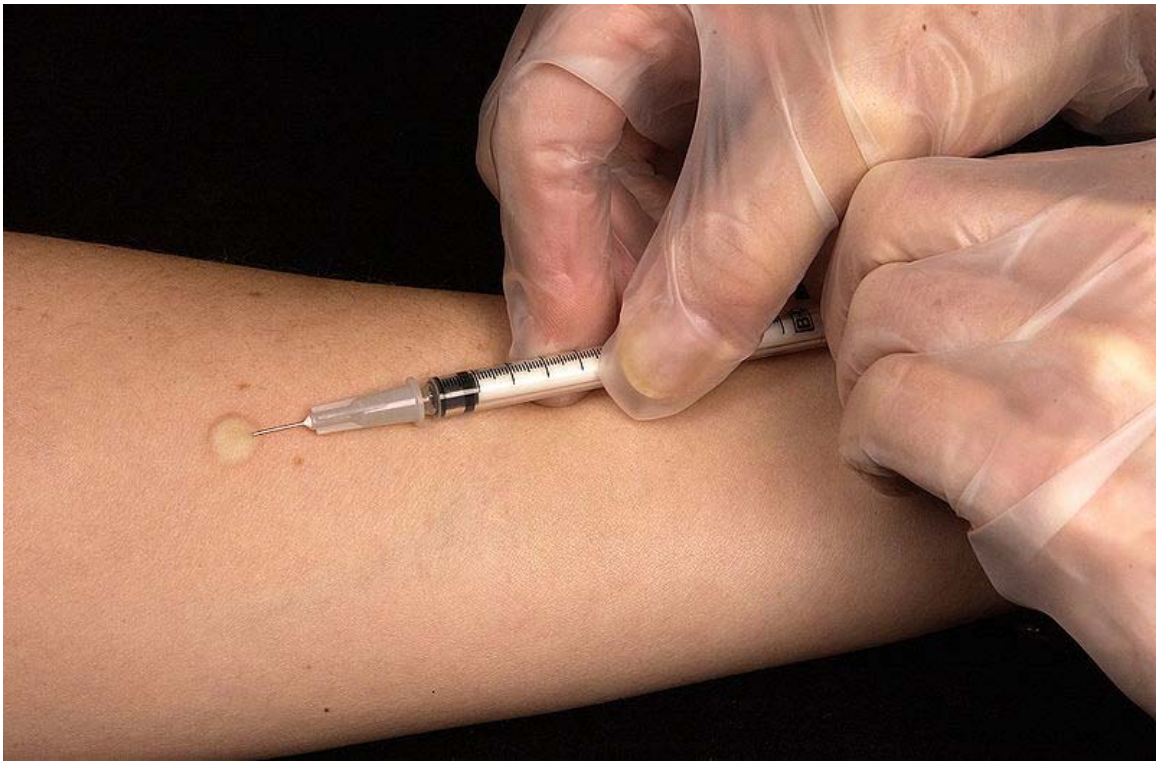
- Infants or children with negative skin test results who are continually exposed to untreated or ineffectively treated patients or will be continually exposed to multidrug-resistant TB.
- Healthcare workers considered on an individual basis in settings in which a high percentage of MDR-TB patients has been found, transmission of MDR-TB is likely, and TB control precautions have been implemented and were not successful.

BCG provides some protection against severe forms of pediatric TB, but has been shown to be unreliable against adult pulmonary TB, which accounts for most of the disease burden worldwide. Currently, there are more cases of TB on the planet than at any other time in history and most agree there is an urgent need for a newer, more effective vaccine that would prevent all forms of TB—including drug resistant strains—in all age groups and among people with HIV.

Several new vaccines to prevent TB infection are being developed. The first recombinant tuberculosis vaccine rBCG30, entered clinical trials in the United States in 2004, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). A 2005 study showed that a DNA TB vaccine given with conventional chemotherapy can accelerate the disappearance of bacteria as well as protect against re-infection in mice; it may take four to five years to be available in humans. A very promising TB vaccine, MVA85A, is currently in phase II trials in South Africa by a group led by Oxford University, and is based on a genetically modified vaccinia virus. Many other strategies are also being used to develop novel vaccines, including both subunit vaccines (fusion molecules composed of two recombinant proteins delivered in an adjuvant) such as Hybrid-1, HyVac4 or M72, and recombinant adenoviruses such as Ad35. Some of these vaccines can be effectively administered without needles, making them preferable for areas where HIV is very common. All of these vaccines have been successfully tested in humans and are now in extended testing in TB-endemic regions. To encourage further discovery, researchers and policymakers are promoting new economic models of vaccine development including prizes, tax incentives and advance market commitments.

January 2011: Statens Serum Institute in Denmark has announced in the journal Nature Medicine that a new vaccine can fight tuberculosis **before** and **after** infection. It has been applied in mice successfully.

Screening



Mantoux tuberculin skin test

Mantoux tuberculin skin tests are often used for routine screening of high risk individuals.

Interferon-γ release assays are blood tests used in the diagnosis of some infectious diseases. There are currently two interferon-γ release assays available for the diagnosis of tuberculosis:

- QuantiFERON-TB Gold (licensed in US, Europe and Japan); and
- T-SPOT.TB, a form of ELISPOT (licensed in Europe).

Chest photofluorography has been used in the past for mass screening for tuberculosis.

Treatment

Treatment for TB uses antibiotics to kill the bacteria. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which makes many antibiotics ineffective and hinders the entry of drugs. The two antibiotics most commonly used are isoniazid and rifampicin. However, instead of the short course of antibiotics typically used to cure other bacterial infections, TB requires much longer periods of treatment (around 6 to 24 months) to entirely eliminate mycobacteria from the body. Latent TB treatment usually uses a single antibiotic, while

active TB disease is best treated with combinations of several antibiotics, to reduce the risk of the bacteria developing antibiotic resistance. People with latent infections are treated to prevent them from progressing to active TB disease later in life.

Drug-resistant tuberculosis is transmitted in the same way as regular TB. Primary resistance occurs in persons infected with a resistant strain of TB. A patient with fully susceptible TB develops secondary resistance (acquired resistance) during TB therapy because of inadequate treatment, not taking the prescribed regimen appropriately, or using low-quality medication. Drug-resistant TB is a public health issue in many developing countries, as treatment is longer and requires more expensive drugs. Multi-drug-resistant tuberculosis (MDR-TB) is defined as resistance to the two most effective first-line TB drugs: rifampicin and isoniazid. Extensively drug-resistant TB (XDR-TB) is also resistant to three or more of the six classes of second-line drugs.

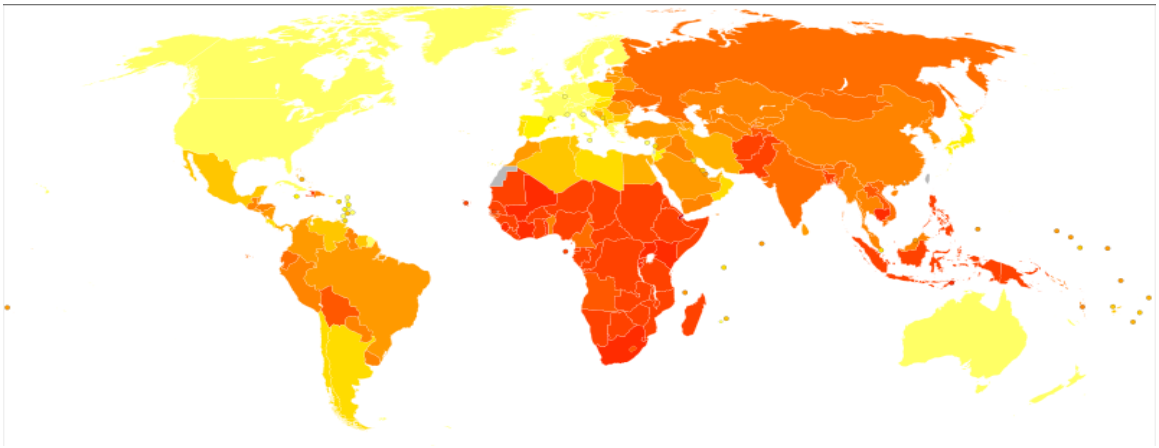
The DOTS (Directly Observed Treatment Short-course) strategy of tuberculosis treatment recommended by WHO was based on clinical trials done in the 1970s by Tuberculosis Research Centre, Chennai, India. The country in which a person with TB lives can determine what treatment they receive. This is because multidrug-resistant tuberculosis is resistant to most first-line medications, the use of second-line antituberculosis medications is necessary to cure the patient. However, the price of these medications is high; thus poor people in the developing world have no or limited access to these treatments.

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.

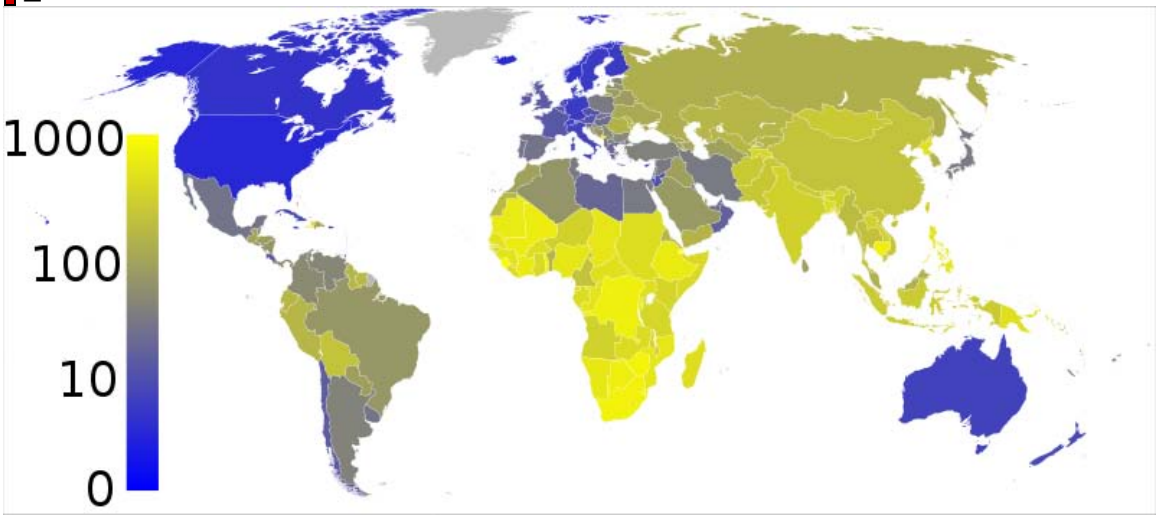
Studies utilizing DNA fingerprinting of *M. tuberculosis* strains have shown that reinfection contributes more substantially to recurrent TB than previously thought, with between 12% and 77% of cases attributable to reinfection (instead of reactivation).

Epidemiology

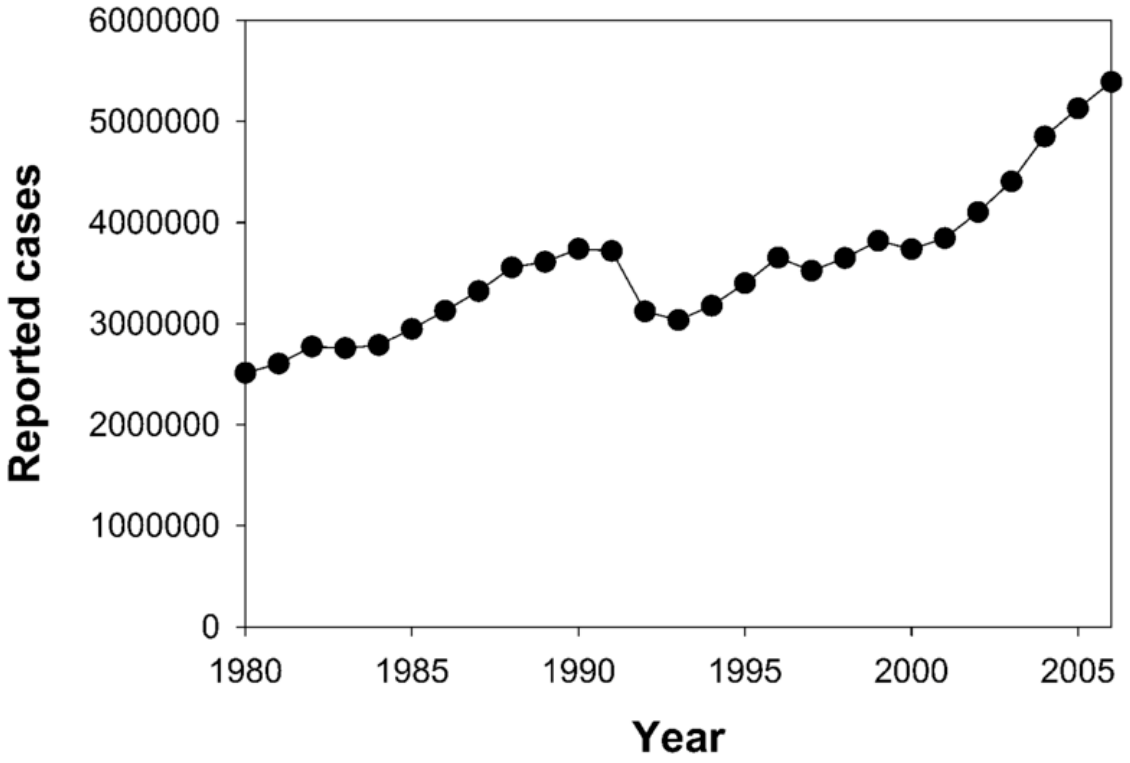


Age-standardized death from tuberculosis per 100,000 inhabitants in 2004.

- no data
- ≤ 10
- 10-25
- 25-50
- 50-75
- 75-100
- 100-250
- 250-500
- 500-750
- 750-1000
- 1000-2000
- 2000-3000
- ≥ 3000



In 2007, the prevalence of TB per 100,000 people was highest in sub-Saharan Africa, and was also relatively high in Asia.



Annual number of new reported TB cases. Data from WHO.

Roughly a third of the world's population has been infected with *M. tuberculosis*, and new infections occur at a rate of one per second. However, not all infections with *M. tuberculosis* cause TB disease and many infections are asymptomatic. In 2007, an estimated 13.7 million people had active TB disease, with 9.3 million new cases and 1.8 million deaths; the annual incidence rate varied from 363 per 100,000 in Africa to 32 per 100,000 in the Americas. Tuberculosis is the world's greatest infectious killer of women of reproductive age and the leading cause of death among people with HIV/AIDS.

The rise in HIV infections and the neglect of TB control programs have enabled a resurgence of tuberculosis. The emergence of drug-resistant strains has also contributed to this new epidemic with, from 2000 to 2004, 20% of TB cases being resistant to standard treatments and 2% resistant to second-line drugs. The rate at which new TB cases occur varies widely, even in neighboring countries, apparently because of differences in health care systems.

In 2007, the country with the highest estimated incidence rate of TB was Swaziland, with 1200 cases per 100,000 people. India had the largest total incidence, with an estimated 2.0 million new cases. The Philippines ranks fourth in the world for the number of cases of tuberculosis and has the highest number of cases per head in Southeast Asia. Almost two thirds of Filipinos have tuberculosis, and up to an additional five million people are infected yearly. In developed countries, tuberculosis is less common and is mainly an urban disease. In the United Kingdom, the national average was 15 per 100,000 in 2007, and the highest incidence rates in Western Europe were 30 per 100,000 in Portugal and

Spain. These rates compared with 98 per 100,000 in China and 48 per 100,000 in Brazil. In the United States, the overall tuberculosis case rate was 4 per 100,000 persons in 2007. In Canada tuberculosis is still endemic in some rural areas.

The incidence of TB varies with age. In Africa, TB primarily affects adolescents and young adults. However, in countries where TB has gone from high to low incidence, such as the United States, TB is mainly a disease of older people, or of the immunocompromised.

There are a number of known factors that make people more susceptible to TB infection: worldwide the most important of these is HIV. Co-infection with HIV is a particular problem in Sub-Saharan Africa, due to the high incidence of HIV in these countries. Smoking more than 20 cigarettes a day also increases the risk of TB by two to four times. Diabetes mellitus is also an important risk factor that is growing in importance in developing countries. Other disease states that increase the risk of developing tuberculosis are Hodgkin lymphoma, end-stage renal disease, chronic lung disease, malnutrition, and alcoholism.

Diet may also modulate risk. For example, among immigrants in London from the Indian subcontinent, vegetarian Hindu Asians were found to have an 8.5 fold increased risk of tuberculosis, compared to Muslims who ate meat and fish daily. Although a causal link is not proved by this data, this increased risk could be caused by micronutrient deficiencies: possibly iron, vitamin B12 or vitamin D. Further studies have provided more evidence of a link between vitamin D deficiency and an increased risk of contracting tuberculosis. Globally, the severe malnutrition common in parts of the developing world causes a large increase in the risk of developing active tuberculosis, due to its damaging effects on the immune system. Along with overcrowding, poor nutrition may contribute to the strong link observed between tuberculosis and poverty.

Prisoners, especially in poor countries, are particularly vulnerable to infectious diseases such as HIV/AIDS and TB. Prisons provide a conditions that allow TB to spread rapidly, due to overcrowding, poor nutrition and a lack of health services. Since the early 1990s, TB outbreaks have been reported in prisons in many countries in Eastern Europe. The prevalence of TB in prisons is much higher than among the general population – in some countries as much as 40 times higher.

History

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. Whether tuberculosis originated in cattle and then transferred to humans, or diverged from a common ancestor infecting a different species, is currently unclear. However, it is clear that *M. tuberculosis* is not directly descended from *M. bovis*, which seems to have evolved relatively recently.

Skeletal remains from a Neolithic Settlement in the Eastern Mediterranean show prehistoric humans (7000 BC) had TB, and tubercular decay has been found in the spines of mummies from 3000–2400 BC. 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. In South America, the earliest evidence of tuberculosis is associated with the Paracas-Caverna culture (circa 750 BC to circa 100 AD). 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."

Other names

In the past, tuberculosis has been called consumption, because it seemed to consume people from within, with a bloody cough, fever, pallor, and long relentless wasting. Other names included *phthisis* (Greek for consumption) and *phthisis pulmonalis*; scrofula (in adults), affecting the lymphatic system and resulting in swollen neck glands; *tabes mesenterica*, TB of the abdomen and *lupus vulgaris*, TB of the skin; wasting disease; white plague, because sufferers appear markedly pale; king's evil, because it was believed that a king's touch would heal scrofula; and Pott's disease, or gibbus of the spine and joints.

Dr. Robert Koch discovered the tuberculosis bacillus

Miliary tuberculosis—now commonly known as disseminated TB—occurs when the infection invades the circulatory system, resulting in millet-like seeding of TB bacilli in the lungs as seen on an X-ray. TB is also called Koch's disease, after the scientist Robert Koch.

Folklore

Before the Industrial Revolution, tuberculosis may sometimes have been regarded as vampirism. When one member of a family died from it, the other members that were infected would lose their health slowly. People believed that this was caused by the original victim draining the life from the other family members. Furthermore, people who had TB exhibited symptoms similar to what people considered to be vampire traits. People with TB often have symptoms such as red, swollen eyes (which also creates a sensitivity to bright light), pale skin, extremely low body heat, a weak heart and coughing blood, suggesting the idea that the only way for the afflicted to replenish this loss of blood was by sucking blood. Another folk belief told that the affected individual was being forced, nightly, to attend fairy revels, so that the victim wasted away owing to lack of rest; this belief was most common when a strong connection was seen between the fairies and the dead. Similarly, but less commonly, it was attributed to the victims being "hagridden"—being transformed into horses by witches (hags) to travel to their nightly meetings, again resulting in a lack of rest.

TB was romanticized in the nineteenth century. Many people believed TB produced feelings of euphoria referred to as *Spes phthisica* ("hope of the consumptive"). It was believed that TB sufferers who were artists had bursts of creativity as the disease progressed. It was also believed that TB sufferers acquired a final burst of energy just before they died that made women more beautiful and men more creative. In the early 20th century, some physicians believed TB to be caused by masturbation.

Study and treatment

The study of tuberculosis, sometimes known as phthisiatry, dates back to *The Canon of Medicine* written by Ibn Sina (Avicenna) in the 1020s. He was the first physician to identify pulmonary tuberculosis as a contagious disease, the first to recognise the association with diabetes, and the first to suggest that it could spread through contact with soil and water. Avicenna adopted, from the Greeks, the theory that epidemics are caused by pollution in the air (*miasma*, a noxious form of "bad air"). He developed the method of quarantine in order to limit the spread of tuberculosis. In ancient times, treatments focused on sufferers' diets. Pliny the Elder described several methods in his *Natural History*: "wolf's liver taken in thin wine, the lard of a sow that has been fed upon grass, or the flesh of a she-ass taken in broth".

Although it was established that the pulmonary form was associated with "tubercles" by Dr Richard Morton in 1689, due to the variety of its symptoms, TB was not identified as a single disease until the 1820s and was not named "tuberculosis" until 1839 by J. L. Schönlein. During the years 1838 – 1845, Dr. John Croghan, the owner of Mammoth

Cave, brought a number of tuberculosis sufferers into the cave in the hope of curing the disease with the constant temperature and purity of the cave air; they died within a year. The first TB sanatorium opened in 1854 in Görbersdorf, Germany (today Sokołowsko, Poland) by Hermann Brehmer.

The bacillus causing tuberculosis, *Mycobacterium tuberculosis*, was identified and described on 24 March 1882 by Robert Koch. He received the Nobel Prize in physiology or medicine in 1905 for this discovery. Koch did not believe that bovine (cattle) and human tuberculosis were similar, which delayed the recognition of infected milk as a source of infection. Later, this source was eliminated by the pasteurization process. Koch announced a glycerine extract of the tubercle bacilli as a remedy for tuberculosis in 1890, calling it "tuberculin". It was not effective, but was later adapted as a test for pre-symptomatic tuberculosis.

The first genuine success in immunizing against tuberculosis was developed from attenuated bovine-strain tuberculosis by Albert Calmette and Camille Guérin in 1906. It was called "BCG" (Bacillus of Calmette and Guérin). The BCG vaccine was first used on humans in 1921 in France, but it was not until after World War II that BCG received widespread acceptance in the USA, Great Britain, and Germany.

Tuberculosis, or "consumption" as it was commonly known, caused the most widespread public concern in the 19th and early 20th centuries as an endemic disease of the urban poor. In 1815, one in four deaths in England was of consumption; by 1918 one in six deaths in France were still caused by TB. In the 20th century, tuberculosis killed an estimated 100 million people. After the establishment in the 1880s that the disease was contagious, TB was made a notifiable disease in Britain; there were campaigns to stop spitting in public places, and the infected poor were pressured to enter sanatoria that resembled prisons; the sanatoria for the middle and upper classes offered excellent care and constant medical attention. Whatever the purported benefits of the fresh air and labor in the sanatoria, even under the best conditions, 50% of those who entered were dead within five years (1916).

The promotion of Christmas Seals began in Denmark during 1904 as a way to raise money for tuberculosis programs. It expanded to the United States and Canada in 1907 – 1908 to help the National Tuberculosis Association (later called the American Lung Association).

In the United States, concern about the spread of tuberculosis played a role in the movement to prohibit public spitting except into spittoons.

In Europe, deaths from TB fell from 500 out of 100,000 in 1850 to 50 out of 100,000 by 1950. Improvements in public health were reducing tuberculosis even before the arrival of antibiotics. The disease remained such a significant threat to public health, that when the Medical Research Council was formed in Britain in 1913, its initial focus was tuberculosis research.

It was not until 1946 with the development of the antibiotic streptomycin that effective treatment and cure became possible. Prior to the introduction of this drug, the only treatment besides sanatoria were surgical interventions, including bronchoscopy and suction as well as the pneumothorax or plombage technique — collapsing an infected lung to "rest" it and allow lesions to heal — a technique that was of little benefit and was mostly discontinued by the 1950s. The emergence of multidrug-resistant TB has again introduced surgery as part of the treatment for these infections. Here, surgical removal of chest cavities will reduce the number of bacteria in the lungs, as well as increasing the exposure of the remaining bacteria to drugs in the bloodstream. It is therefore thought to increase the effectiveness of the chemotherapy.

Hopes that the disease could be completely eliminated have been dashed since the rise of drug-resistant strains in the 1980s. For example, tuberculosis cases in Britain, numbering around 117,000 in 1913, had fallen to around 5,000 in 1987, but cases rose again, reaching 6,300 in 2000 and 7,600 cases in 2005. Due to the elimination of public health facilities in New York and the emergence of HIV, there was a resurgence of TB in the late 1980s. The number of patients failing to complete their course of drugs is high. New York had to cope with more than 20,000 TB patients with multidrug-resistant strains (resistant to, at least, both Rifampin and Isoniazid).

The resurgence of tuberculosis resulted in the declaration of a global health emergency by the World Health Organization (WHO) in 1993. Every year, nearly half a million new cases of multidrug-resistant tuberculosis (MDR-TB) are estimated to occur worldwide.

Age

Tuberculosis has been around for millennia. The oldest known human remains showing signs of tuberculosis infection are 9,000 years old. During this period, *M. tuberculosis* has lost numerous coding and non-coding regions in its genome, losses that can be used to distinguish between strains of the bacteria. The implication is that *M. tuberculosis* strains differ geographically, so their genetic differences can be used to track the origins and movement of each strain.

A new species has recently been discovered for the first time in 20 years.

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*.

In other animals

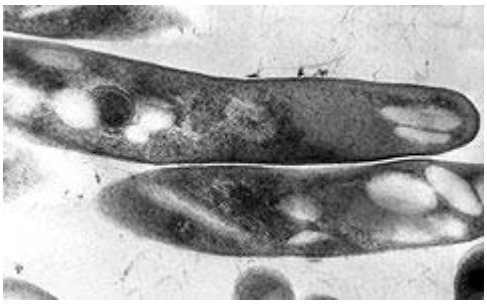
Tuberculosis can be carried by mammals; domesticated species, such as cats and dogs, are generally free of tuberculosis, but wild animals may be carriers.

Mycobacterium bovis causes TB in cattle. An effort to eradicate bovine tuberculosis from the cattle and deer herds of New Zealand is underway. It has been found that herd infection is more likely in areas where infected natural reservoir such as Australian brush-tailed possums come into contact with domestic livestock at farm/bush borders. Controlling the vectors through possum eradication and monitoring the level of disease in livestock herds through regular surveillance are seen as a "two-pronged" approach to ridding New Zealand of the disease.

In Ireland and the United Kingdom, badgers have been identified as one vector species for the transmission of bovine tuberculosis. As a result, governments have come under pressure from some quarters, primarily dairy farmers, to mount an active campaign of eradication of badgers in certain areas with the purpose of reducing the incidence of bovine TB. The effectiveness of culling on the incidence of TB in cattle is a contentious issue, with proponents and opponents citing their own studies to support their position. For instance, a study by an Independent Study Group on badger culling reported on 18 June 2007 that it was unlikely to be effective and would only make a “modest difference” to the spread of TB and that "badger culling cannot meaningfully contribute to the future control of cattle TB"; in contrast, another report concluded that this policy would have a significant impact. On 4 July 2008, the UK government decided against a proposed random culling policy.

Chapter 2

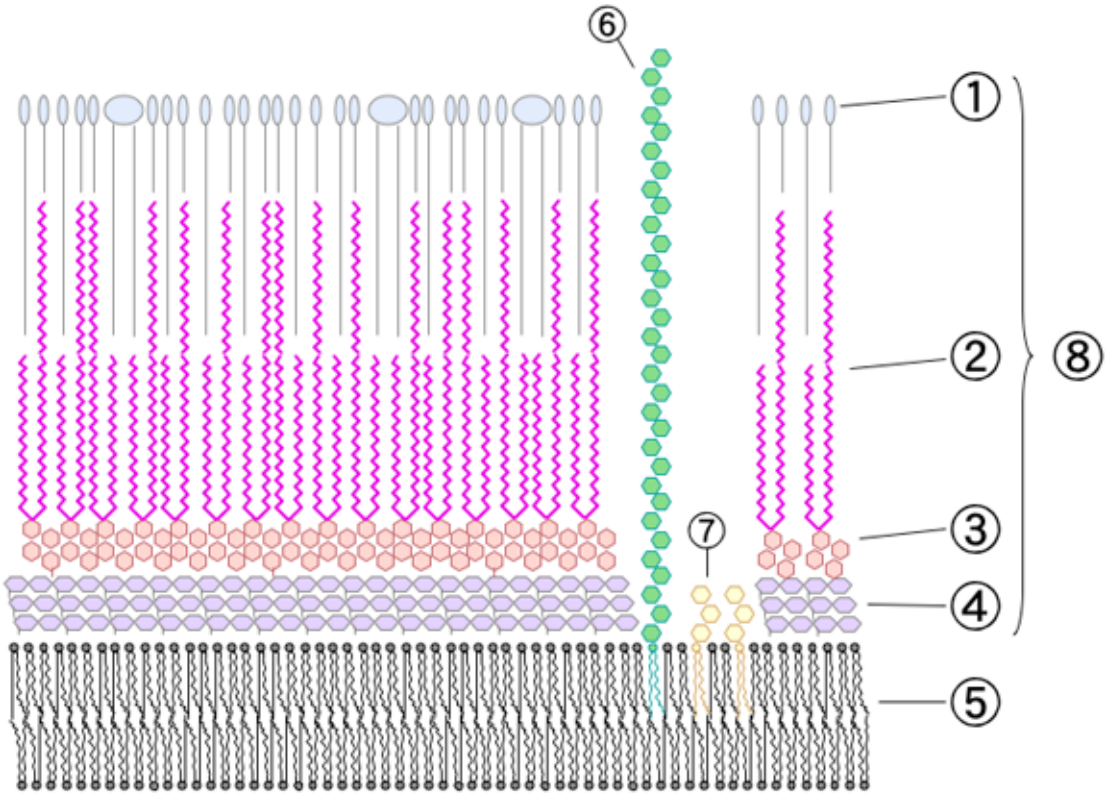
Mycobacterium

Mycobacterium

TEM micrograph of *M. tuberculosis*.
Scientific classification

Kingdom:	Bacteria
Phylum:	Actinobacteria
Order:	Actinomycetales
Suborder:	Corynebacterineae
Family:	**Mycobacteriaceae**
Genus:	***Mycobacterium*** Lehmann & Neumann 1896

Mycobacterium is a genus of Actinobacteria, given its own family, the Mycobacteriaceae. The genus includes pathogens known to cause serious diseases in mammals, including tuberculosis (*Mycobacterium tuberculosis*) and leprosy (*Mycobacterium leprae*). The Latin prefix *"myco—"* means both *fungus* and *wax*; its use here reflects the "waxy" compounds that compose parts of the cell wall**.**

Microbiologic characteristics



Mycobacterial cell wall: 1-outer lipids, 2-mycolic acid, 3-polysaccharides (arabinogalactan), 4-peptidoglycan, 5-plasma membrane, 6-lipoarabinomannan (LAM), 7-phosphatidylinositol mannoside, 8-cell wall skeleton

Mycobacteria are aerobic and nonmotile bacteria (except for the species *Mycobacterium marinum*, which has been shown to be motile within macrophages) that are characteristically acid-alcohol fast. Mycobacteria do not contain endospores or capsules and are usually considered Gram-positive. A recent paper in PNAS showed sporulation in *Mycobacterium marinum* and perhaps in *M. bovis* . However, this has been strongly argued by other scientists . While mycobacteria do not seem to fit the Gram-positive category from an empirical standpoint (i.e. they generally do not retain the crystal violet stain well), they are classified as an acid-fast Gram-positive bacterium due to their lack of an outer cell membrane. All *Mycobacterium* species share a characteristic cell wall, thicker than in many other bacteria, which is hydrophobic, waxy, and rich in mycolic acids/mycolates. The cell wall consists of the hydrophobic mycolate layer and a peptidoglycan layer held together by a polysaccharide, arabinogalactan. The cell wall makes a substantial contribution to the hardiness of this genus. The biosynthetic pathways of cell wall components are potential targets for new drugs for tuberculosis.

Many *Mycobacterium* species adapt readily to growth on very simple substrates, using ammonia or amino acids as nitrogen sources and glycerol as a carbon source in the

presence of mineral salts. Optimum growth temperatures vary widely according to the species and range from 25 °C to over 50 °C.

Some species can be very difficult to culture (i.e. they are fastidious), sometimes taking over two years to develop in culture. Further, some species also have extremely long reproductive cycles — *M. leprae*, may take more than 20 days to proceed through one division cycle (for comparison, some *E. coli* strains take only 20 minutes), making laboratory culture a slow process. In addition, the availability of genetic manipulation techniques still lags far behind that of other bacterial species.

A natural division occurs between slowly– and rapidly–growing species. Mycobacteria that form colonies clearly visible to the naked eye within seven days on subculture are termed rapid growers, while those requiring longer periods are termed slow growers. Mycobacteria cells are straight or slightly curved rods between 0.2-0.6 μm wide by 1.0-10 μm long.

Pigmentation

Some mycobacteria produce carotenoid pigments without light. Others require photoactivation for pigment production.

Photochromogens (Group I)
: Produce nonpigmented colonies when grown in the dark and pigmented colonies only after exposure to light and reincubation.

- Ex: *M. kansasii*, *M. marinum*, *M. simiae*.

Scotochromogens (Group II)
: Produce deep yellow to orange colonies when grown in the presence of either the light or dark.

- Ex: *M. scrofulaceum*, *M. gordonae*, *M. xenopi*, *M. szulgai*.

Non-chromogens (Groups III & IV)
: Nonpigmented in the light and dark or have only a pale yellow, buff or tan pigment that does not intensify after light exposure.

- Ex: *M. tuberculosis*, *M. avium-intra-cellulare*, *M. bovis*, *M. ulcerans*
- Ex: *M. fortuitum*, *M. chelonae*

Staining characteristics

Mycobacteria are classical acid-fast organisms. Stains used in evaluation of tissue specimens or microbiological specimens include Fite's stain, Ziehl-Neelsen stain, and Kinyoun stain.

Mycobacteria appear phenotypically most closely related to members of *Nocardia*, *Rhodococcus* and *Corynebacterium*.

Ecological characteristics

Mycobacteria are widespread organisms, typically living in water (including tap water treated with chlorine) and food sources. Some, however, including the tuberculosis and the leprosy organisms, appear to be obligate parasites and are not found as free-living members of the genus.

Pathogenicity

Mycobacteria can colonize their hosts without the hosts showing any adverse signs. For example, billions of people around the world have asymptomatic infections of *M. tuberculosis*.

Mycobacterial infections are notoriously difficult to treat. The organisms are hardy due to their cell wall, which is neither truly Gram negative nor positive. Additionally, they are naturally resistant to a number of antibiotics that disrupt cell-wall biosynthesis, such as penicillin. Due to their unique cell wall, they can survive long exposure to acids, alkalis, detergents, oxidative bursts, lysis by complement, and many antibiotics. Most mycobacteria are susceptible to the antibiotics clarithromycin and rifamycin, but antibiotic-resistant strains have emerged.

As with other bacterial pathogens, surface and secreted proteins of *M. tuberculosis* contribute significantly to the virulence of this organism. There is an increasing list of extracytoplasmic proteins proven to have a function in the virulence of *M. tuberculosis*.

Medical classification

Mycobacteria can be classified into several major groups for purpose of diagnosis and treatment: *M. tuberculosis* complex, which can cause tuberculosis: *M. tuberculosis, M. bovis, M. africanum, and M. microti*; *M. leprae*, which causes Hansen's disease or leprosy; Nontuberculous mycobacteria **(NTM)** are all the other mycobacteria, which can cause pulmonary disease resembling tuberculosis, lymphadenitis, skin disease, or disseminated disease.

Phenotypic testing

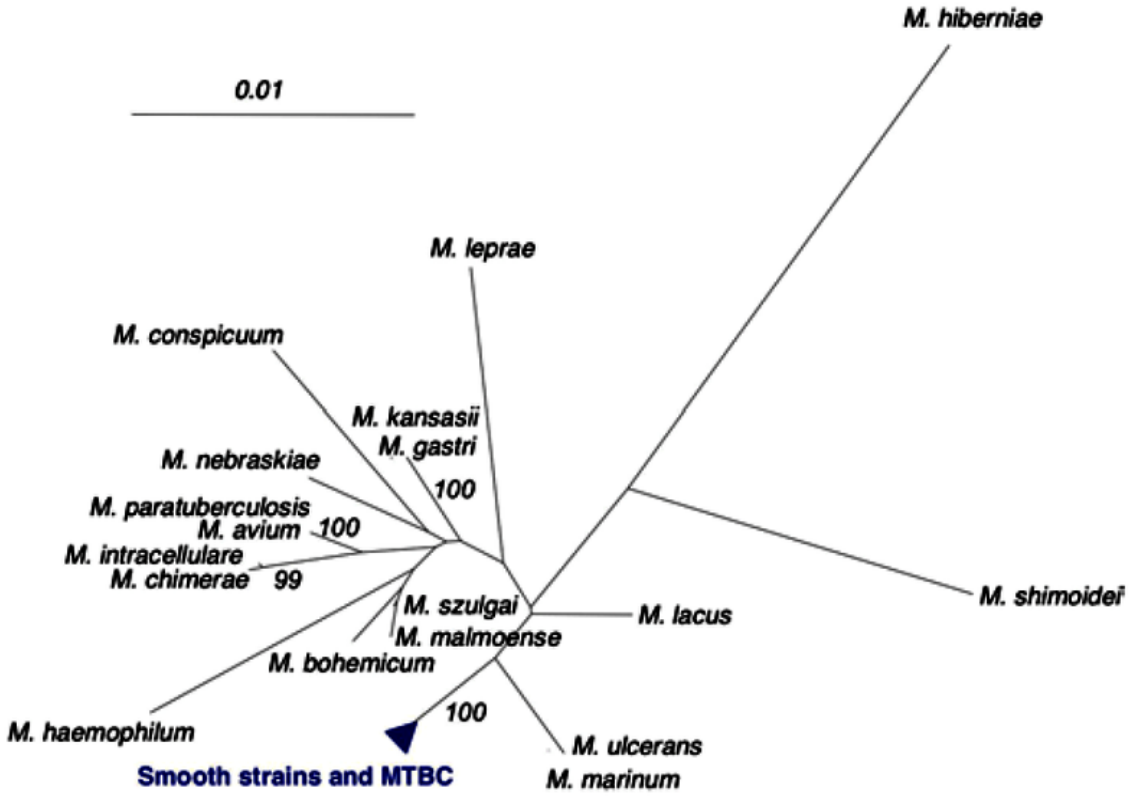
Various phenotypic tests can be used to identify and distinguish different Mycobacteria species and strains.

Phenotypic testing of Mycobacteria

Mycosides

Mycosides are phenolic alcohols (such as phenolphthiocerol) that were shown to be components of mycobacterium glycolipids that are termed glycosides of phenolphthiocerol dimycocerosate (Smith DW et al., Nature 1960, 186, 887) There are 18 and 20 carbon atoms in mycosides A, and B, respectively.

Species



Phylogenetic Position of the Tubercle Bacilli within the Genus Mycobacterium The blue triangle corresponds to tubercle bacilli sequences that are identical or differing by a single nucleotide. The sequences of the genus Mycobacterium that matched most closely to those of M. tuberculosis were retrieved from the BIBI database and aligned with those obtained for 17 smooth and MTBC strains. The unrooted neighbor-joining tree is based on 1,325 aligned nucleotide positions of the 16S rRNA gene. The scale gives the pairwise distances after Jukes-Cantor correction. Bootstrap support values higher than 90% are indicated at the nodes.

In older systems, mycobacteria are grouped based upon their appearance and rate of growth. However, these are symplesiomorphies, and more recent classification is based upon cladistics.

Slowly growing

Mycobacterium tuberculosis complex

- *Mycobacterium tuberculosis complex* (MTBC) members are causative agents of human and animal tuberculosis. Species in this complex include:

  M. tuberculosis, the major cause of human tuberculosis
  M. bovis
  M. bovis BCG
  M. africanum
  M. canetti
  M. caprae
  M. microti
  M. pinnipedii

Mycobacterium avium complex

- *Mycobacterium avium complex (MAC),* is a group of species that, in a disseminated infection but not lung infection, used to be a significant cause of death in AIDS patients. Species in this complex include:

  M. avium
  M. avium paratuberculosis, which has been implicated in Crohn's disease in humans and Johne's disease in cattle and sheep
  M. avium silvaticum
  M. avium "hominissuis"
  M. colombiense

Mycobacterium gordonae clade

- *M. asiaticum*
- *M. gordonae*

Mycobacterium kansasii clade

- *M. gastri*
- *M. kansasii*

Mycobacterium nonchromogenicum/terrae clade

- *M. hiberniae*
- *M. nonchromogenicum*
- *M. terrae*
- *M. triviale*

Mycolactone-producing mycobacteria

- *M. ulcerans*, which causes the "Buruli", or "Bairnsdale, ulcer"
- *M. pseudoshottsii*
- *M. shottsii*

Mycobacterium simiae clade

- *M. triplex*
- *M. genavense*
- *M. florentinum*
- *M. lentiflavum*
- *M. palustre*
- *M. kubicae*
- *M. parascrofulaceum*
- *M. heidelbergense*
- *M. interjectum*
- *M. simiae*

Ungrouped

- *M. branderi*
- *M. cookii*
- *M. celatum*
- *M. bohemicum*
- *M. haemophilum*
- *M. malmoense*
- *M. szulgai*
- *M. leprae*, which causes leprosy
- *M. lepraemurium*
- *M. lepromatosis*, another (less significant) cause of leprosy, described in 2008
- *M. africanum*
- *M. botniense*
- *M. chimaera*
- *M. conspicuum*
- *M. doricum*
- *M. farcinogenes*
- *M. heckeshornense*
- *M. intracellulare*
- *M. lacus*
- *M. marinum*
- *M. monacense*
- *M. montefiorense*
- *M. murale*
- *M. nebraskense*
- *M. saskatchewanense*

- *M. scrofulaceum*
- *M. shimoidei*
- *M. tusciae*
- *M. xenopi*

Intermediate growth rate

- *M. intermedium*

Rapidly growing

Mycobacterium chelonae clade

- *M. abscessus*
- *M. chelonae*
- *M. bolletii*

Mycobacterium fortuitum clade

- *M. fortuitum*
- *M. fortuitum subsp. acetamidolyticum*
- *M. boenickei*
- *M. peregrinum*
- *M. porcinum*
- *M. senegalense*
- *M. septicum*
- *M. neworleansense*
- *M. houstonense*
- *M. mucogenicum*
- *M. mageritense*
- *M. brisbanense*
- *M. cosmeticum*

Mycobacterium parafortuitum clade

- *M. parafortuitum*
- *M. austroafricanum*
- *M. diernhoferi*
- *M. hodleri*
- *M. neoaurum*
- *M. frederiksbergense*

Mycobacterium vaccae clade

- *M. aurum*

- *M. vaccae*

CF

- *M. chitae*
- *M. fallax*

Ungrouped

- *M. confluentis*
- *M. flavescens*
- *M. madagascariense*
- *M. phlei*
- *M. smegmatis*
    - *M. goodii*
    - *M. wolinskyi*
- *M. thermoresistibile*
- *M. gadium*
- *M. komossense*
- *M. obuense*
- *M. sphagni*
- *M. agri*
- *M. aichiense*
- *M. alvei*
- *M. arupense*
- *M. brumae*
- *M. canariasense*
- *M. chubuense*
- *M. conceptionense*
- *M. duvalii*
- *M. elephantis*
- *M. gilvum*
- *M. hassiacum*
- *M. holsaticum*
- *M. immunogenum*
- *M. massiliense*
- *M. moriokaense*
- *M. psychrotolerans*
- *M. pyrenivorans*
- *M. vanbaalenii*
- *M. pulveris*

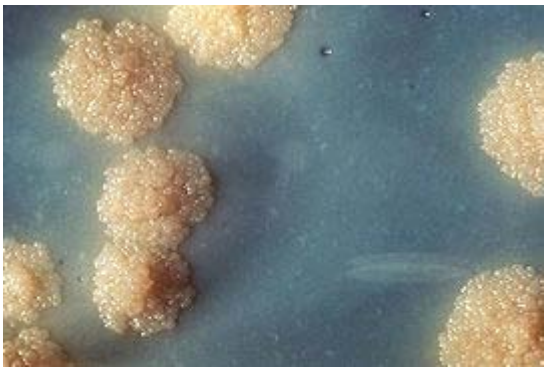
Ungrouped

- *M. arosiense*
- *M. aubagnense*

- *M. caprae*
- *M. chlorophenolicum*
- *M. fluoroanthenivorans*
- *M. kumamotonense*
- *M. novocastrense*
- *M. parmense*
- *M. phocaicum*
- *M. poriferae*
- *M. rhodesiae*
- *M. seoulense*
- *M. tokaiense*

Chapter 3

Mycobacterium Tuberculosis

Mycobacterium tuberculosis

M. tuberculosis bacterial colonies
Scientific classification
Kingdom: Bacteria
Phylum: Actinobacteria
Order: Actinomycetales
Suborder: Corynebacterineae
Family: Mycobacteriaceae
Genus: *Mycobacterium*
Species: ***M. tuberculosis***
Binomial name
Mycobacterium tuberculosis Zopf 1883
Synonyms
Tubercle bacillus Koch 1882

Mycobacterium tuberculosis (MTB) is a pathogenic bacterial species in the genus *Mycobacterium* and the causative agent of most cases of tuberculosis. First discovered in 1882 by Robert Koch, *M. tuberculosis* has an unusual, waxy coating on the cell surface (primarily mycolic acid), which makes the cells impervious to Gram staining so acid-fast detection techniques are used instead. The physiology of *M. tuberculosis* is highly aerobic and requires high levels of oxygen. Primarily a pathogen of the mammalian

respiratory system, MTB infects the lungs and is the causative agent of tuberculosis.The most frequently used diagnostic methods for TB are the tuberculin skin test, acid-fast stain, and chest radiographs.

The *M. tuberculosis* genome was sequenced in 1998.

Pathophysiology

M. tuberculosis requires oxygen to grow. It does not retain any bacteriological stain due to high lipid content in its wall, and thus is neither Gram positive nor Gram negative; hence Ziehl-Neelsen staining, or acid-fast staining, is used. While Mycobacteria do not seem to fit the Gram-positive category from an empirical standpoint (i.e., they do not retain the crystal violet stain), they are classified as acid-fast Gram-positive bacteria due to their lack of an outer cell membrane.

M. tuberculosis divides every 15–20 hours, which is extremely slow compared to other bacteria, which tend to have division times measured in minutes (*Escherichia coli* (*E. coli*) can divide roughly every 20 minutes). It is a small bacillus that can withstand weak disinfectants and can survive in a dry state for weeks. Its unusual cell wall, rich in lipids (e.g., mycolic acid), is likely responsible for this resistance and is a key virulence factor.

When in the lungs, *M. tuberculosis* is taken up by alveolar macrophages, but they are unable to digest the bacterium. Its cell wall prevents the fusion of the phagosome with a lysosome. Specifically, *M. tuberculosis* blocks the bridging molecule, early endosomal autoantigen 1 (EEA1); however, this blockade does not prevent fusion of vesicles filled with nutrients. Consequently, the bacteria multiply unchecked within the macrophage. The bacteria also carried the *UreC* gene, which prevents acidification of the phagosome. The bacteria also evade macrophage-killing by neutralizing reactive nitrogen intermediates.

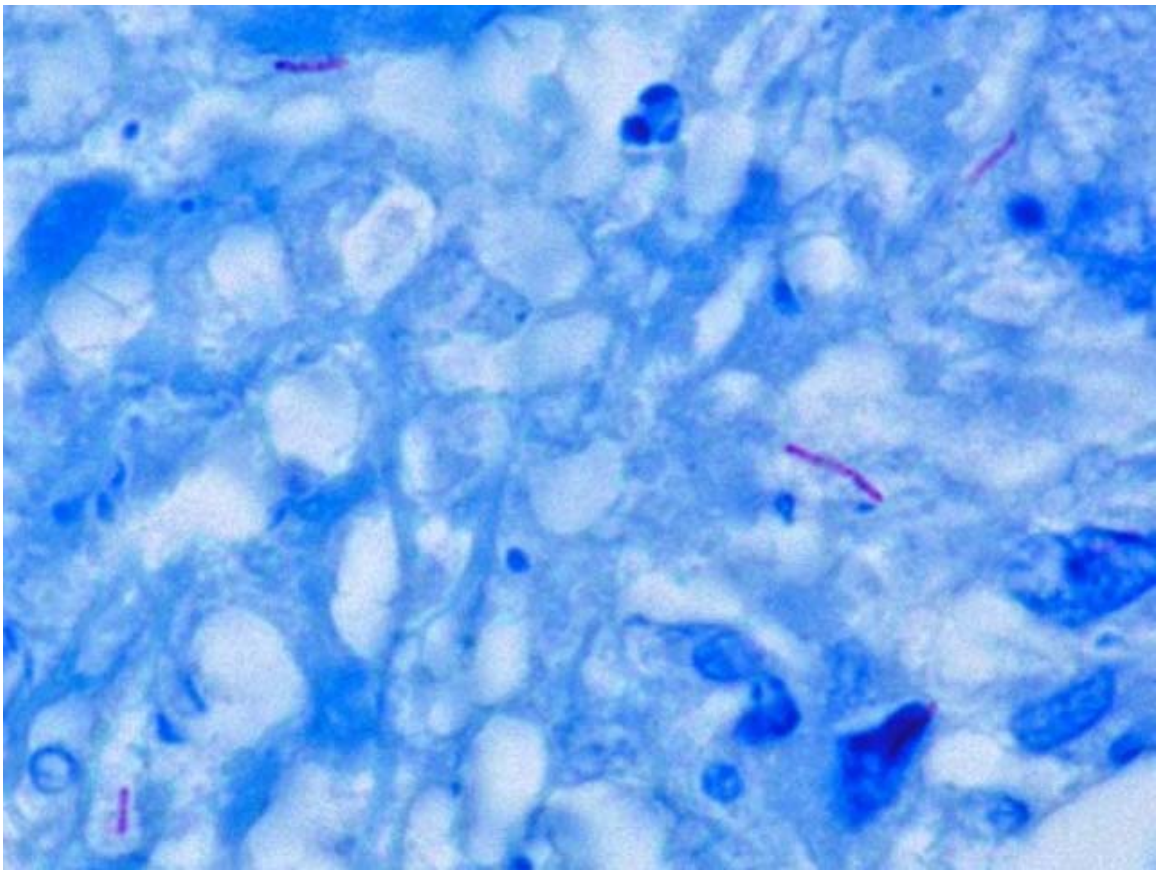
The ability to construct *M. tuberculosis* mutants and test individual gene products for specific functions has significantly advanced our understanding of the pathogenesis and virulence factors of *M. tuberculosis*. Many secreted and exported proteins are known to be important in pathogenesis.

Strain variation

M. tuberculosis Comes from the genus *Mycobacterium,*which is composed of approximately 100 recognized and proposed species. The most familiar of the species are *Mycobacterium tuberculosis* and *Mycobacterium leprae*(Leprosy). *M. tuberculosis* appears to be genetically diverse. A genetic diversity results in significant phenotypic differences between clinical isolates. *M. tuberculosis* exhibits a biogeographic population structure and different strain lineages are associated with different geographic regions. Phenotypic studies suggest that this strain variation never has implications for the development of new diagnostics and vaccines. Micro-evolutionary variation affects the relative fitness and transmission dynamics of antibiotic-resistant strains.

Hypervirulent strains

Mycobacterium outbreaks are often caused by hypervirulent strains of *M. tuberculosis*. In laboratory experiments, these clinical isolates elicit unusual immunopathology and may be either hyperinflammatory or hypoinflammatory. Studies have shown that the majority of hypervirulent mutants have deletions in their cell wall modifying enzymes or regulators that respond to environmental stimuli. Studies of these mutants have indicated the mechanisms that enable *M. tuberculosis* to mask its full pathogenic potential, inducing a granuloma that provides a protective niche and enables the bacilli to sustain a long-term persistent infection.



Mycobacterium tuberculosis *(stained red) in tissue (blue)*

Microscopy

M. tuberculosis is characterized by caseating granulomas containing Langhans giant cells, which have a "horseshoe" pattern of nuclei. Organisms are identified by their red color on acid-fast staining.

Genome

The genome of the H37Rv strain was published in 1998. Its size is 4 million base pairs, with 3959 genes. 40% of these genes have had their function characterised, with possible function postulated for another 44%. Within the genome are also 6 pseudogenes.

The genome contains 250 genes involved in fatty acid metabolism, with 39 of these involved in the polyketide metabolism generating the waxy coat. Such large numbers of conserved genes shows the evolutionary importance of the waxy coat to pathogen survival.

10% of the coding capacity is taken up by 2 clustered gene families that encode acidic glycine rich proteins. These proteins have a conserved N-terminal motif, deletion of which impairs growth in macrophages and granulomas.

Nine non-coding sRNAs have been characterised in *M. tuberculosis* with a further 56 predicted in a bioinformatics screen.

Symptoms

It is estimated that only about 10% of people infected with M. tuberculosis ever develop tuberculosis disease and many of those have the disease only for the first few years following infection even though the bacillus may lie dormant in the body for decades.

The symptoms that patients infected with M. tuberculosis may experience are usually absent until the disease has become more complicated. It may take many months from the time the infection initially gets into the lungs until symptoms develop. Cough is however the first symptom of the infection with M. tuberculosis. The initial symptoms, including loss of appetite, fever, productive cough and loss of energy or loss of weight or night sweats are not specific and might be easily attributed to another condition.

Primary pulmonary tuberculosis is the first stage of the condition and it may cause fever, dry cough and some abnormalities that may be noticed on a chest x-ray. However, in most cases, primary infections tend to cause no symptoms that people do not overcome. This condition resolves itself although it returns in more than half cases.

Tuberculosis causing lung disease may result in tuberculous pleuritis, a condition that may cause symptoms such as chest pain, nonproductive cough and fever. Moreover, infection with M. tuberculosis can spread to other parts of the body, especially in patients with a weakened immune system. This condition is referred to as miliary tuberculosis and people contacting it may experience fever, weight loss, weakness and a poor appetite. In more rare cases, miliary tuberculosis can cause cough and difficulty breathing.

Dormant (inactive) tuberculosis may return after a certain period of time and it usually occurs in the upper lungs causing severe symptoms such as common cough with a

progressive increase in production of mucus and coughing up blood. Most patients also develop fever, loss of appetite, unexplained weight loss and night sweats.

In cases in which the infection spreads to other parts of the body, additional symptoms may occur, depending on the exact site of the spread. If the infection spreads to the abdominal cavity, symptoms such as fatigue, swelling, slight tenderness and appendicitis-like pain are likely to occur. Also, painful urination might be a sign that the infection has reached the bladder. In children, M. tuberculosis infections may affect the bones causing mild swelling and minimal pain. Fever, headache, nausea, drowsiness, and, if untreated, coma and brain damage may occur if the brain has been affected. If the infection affects the pericardium, symptoms and signs such as fever, enlarged neck veins, and shortness of breath may develop. Kidney damage and the symptoms emerging with it as well as sterility may occur if the kidney, respectively the reproductive system are affected.

Diagnosis

Sputum is taken on three successive mornings as the number of organisms could be low, and the specimen is treated with 3% KOH or NaOH for liquefaction and decontamination. Gram stain should never be performed, as the organism is an "acid-fast bacillus" (AFB), meaning that it retains certain stains after being treated with acidic solution. In the most common staining technique, the Ziehl-Neelsen stain, AFB are stained a bright red, which stands out clearly against a blue background; therefore, the bacteria are sometimes called *red snappers*. The reason for the acid-fast staining is because of its thick waxy cell wall. The waxy quality of the cell wall is mainly due to the presence of mycolic acids. This waxy cell wall also is responsible for the typical caseous granuloma formation in tuberculosis. The component responsible, trehalose dimycolate, is called the cord factor. A grading system exists for interpretation of the microscopic findings based on the number of organisms observed in each field. Patients of pulmonary tuberculosis show AFB (acid fast bacillus) in their sputum in only 50% of cases, which means that, even if no organisms are observed, further investigation is still required. Acid-fast bacilli can also be visualized by fluorescent microscopy using auramine-rhodamine stain for screening, which makes them appear somewhat golden in color. Also, *M. tuberculosis* is grown on a selective medium known as Lowenstein-Jensen medium, which has traditionally been used for this purpose. However, this method is quite slow, as this organism requires 6–8 weeks to grow, which delays reporting of results. A faster result can now be obtained using Middlebrook medium or BACTEC.

It should be taken into consideration that during an advanced stage of tuberculosis, the organism may infect almost any part of the body, which means that a specimen should appropriately be chosen (e.g. intestinal tuberculosis-stool).

An immunochromatographic serological essay for the diagnosis of *M. tuberculosis* has also been developed.

Treatment

Treatment is usually administered on an outpatient basis and it consists mainly of medication. Usually, the treatment is given for six to nine months according to a therapy regimen consisting of two months of isoniazid, rifampin, and pyrazinamide, four months of isoniazid and rifampin and ethambutol or streptomycin until the drug sensitivity is known. The drug treatment schema may be changed according to the laboratory results.

Antibiotics are usually part of therapy in people who have no symptoms and whose germs are in inactive state. Antibiotics in this case are helpful in preventing the activation of the infection. The antibiotic used for this purpose is called isoniazid (INH). If taken for six to 12 months, it will prevent the tuberculosis from becoming active in the future. This medicine may not however be taken during pregnancy or in people who suffer from liver disease or alcoholism. Moreover, several side effects have been reported to this drug and some of them can be even life-threatening. One of the side effects caused by this drug is peripheral neuropathy, meaning a decreased sensation in the extremities and which is normally prevented or avoided by administering vitamin B6 at the same time with isoniazid.

Patients who have active bacteria are usually treated with a combination of medications, at the same time with the main antibiotic, isoniazid. The main drugs used in conjunction with isoniazid are rifampin, ethambutol and pyrazinamide.

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").

Usually treatment lasts for few months but it can even be administered for years, in some cases. Mainly, the rate of success of the treatment is in close relation with the patient's compliance and ability to take the drugs as prescribed.

History

M. tuberculosis, then known as the *tubercle bacillus*, was first described on 24 March 1882 by Robert Koch, who subsequently received the Nobel Prize in physiology or medicine for this discovery in 1905; the bacterium is also known as *Koch's bacillus*.

Infections with tuberculosis have always been existent although their names have constantly changed over the time. However, it is not until 1720 that the history of tuberculosis starts to take shape into what is known of it today as the physician Benjamin Marten describes in his A Theory of Consumption that tuberculosis may be caused by small living creatures that are transmitted through the air to other patients.

Chapter 4

Latent Tuberculosis

Latent tuberculosis	
ICD-10	R76.1
ICD-9	795.5

Also called **latent tuberculosis** infection, latent TB or LTBI.

Latent tuberculosis is where a patient is infected with *Mycobacterium tuberculosis*, but does not have active tuberculosis disease. Patients with latent tuberculosis are not infectious, and it is not possible to get TB from someone with latent tuberculosis. The main risk is that approximately 10% (5% in the first 2 years after infection and 0.1% per year thereafter but higher risk if immunosuppressed) of these patients will go on to develop active tuberculosis at a later stage of their life. The identification and treatment of people with latent TB is an important part of controlling this disease.

Tests for latent tuberculosis

There are currently two major classes of tests used to identify patients with latent tuberculosis: tuberculin skin tests and γ-interferon tests. The tuberculin skin tests in use include (but are not limited to)

- Mantoux test
- Heaf test
- Tine test (often misspelled as tyne)

There are currently three γ-interferon (interferon gamma release assay - IGRA) tests available.

- T-SPOT.TB
- QuantiFERON-TB Gold
- QuantiFERON-TB Gold In-Tube

A description of the tests and their interpretation is given below.

Tuberculin skin testing

The tuberculin skin test has its origins in the late 19th century. Crudely speaking, tuberculin (also called purified protein derivative or PPD) is a standardised killed extract of cultured TB, injected into the skin to measure the reaction that person's immune response to TB. There are three methods of testing, the Mantoux test, the Heaf test and the Tine test. The Heaf test was preferred in the UK because it requires less training to administer and because there is less interobserver variation in its interpretation. The Heaf test was stopped in 2005 because the manufacturer did not find it financially sustainable to continue manufacturing the test.

Mantoux test

The Mantoux test is now standardised by the WHO. 0.1 ml of tuberculin (100 units/ml) is given by intradermal injection into the volar surface of the forearm (subcutaneous injection results in false negative results). A waterproof ink mark is drawn around the injection site so as to avoid difficulty finding it later if the level of reaction is small. The test is read two to seven days afterwards. The area of induration (NOT erythema) is measured transversely across the forearm (left to right, not up and down) and recorded to the nearest millimetre.

Heaf test

The Heaf test was first described in 1951 (Heaf 1951, pp. 151–3). The test uses a Heaf gun with disposable single-use heads; each head has six needles arranged in a circle. There are standard heads and pediatric heads: the standard head is used on all patients aged 2 years and older; the pediatric head is for infants under the age of 2. For the standard head, the needles protrude 2 mm when the gun is actuated; for the pediatric heads, the needles protrude 1 mm. Skin is cleaned with alcohol, then tuberculin (100,000 units/ml) is evenly smeared on the skin (about 0.1 ml); the gun is then applied to the skin and fired. The excess solution is then wiped off and a waterproof ink mark is drawn around the injection site. The test is read 2 to 7 days later.

- Grade 0: no reaction, or induration of 3 or less puncture points;
- Grade 1: induration of four or more puncture points;
- Grade 2: induration of the six puncture points coalesce to form a circle;
- Grade 3: induration of 5 mm; or more
- Grade 4: induration of 10 mm or more, or ulceration

It is not easy to translate between Heaf and Mantoux, but

- Heaf grade 0 & 1 ~ Mantoux less than 5 mm;
- Heaf grade 2 ~ Mantoux 5–14 mm;
- Heaf grade 3 & 4 ~ Mantoux 15 or greater

The tuberculin used for Heaf tests is 1000 times more concentrated than that used for Mantoux tests. In countries where both tests are used, use of the correct concentration avoids false positive and false negative results.

Tuberculin conversion

Tuberculin conversion is said to occur if a patient who has previously had a negative tuberculin skin test develops a positive tuberculin skin test at a later date. This is strong evidence for significant exposure to TB. The UK recommendation is that the two tests be done at least six weeks apart; the U.S. recommendation is that the two tests can be done as little as one week apart.

Boosting

The phenomenon of **boosting** occurs when people who have had previous exposure to Bacille Calmette Guerin of Mycobacterium bovis (BCG), an attenuated strain of Mycobacterium bovis that is used in some countries as a vaccine against tuberculosis are given repeated tuberculin skin tests. In these people, the first test revives or primes the immune response so that on repeat testing, the response is much stronger and the patient then looks as if he now has a positive reaction. The second tuberculin skin test result is the correct one.

The UK and U.S. guidelines approach the phenomenon of boosting differently. Under U.S. guidelines, which say to ignore previous immunisation with BCG, a person showing the phenomenon of boosting will be falsely described as a tuberculin converter. On the other hand, UK guidelines advise two tuberculin skin tests one week apart if boosting is suspected, taking the result of the second test as being the true result.

Boosting can occur up to two years after the first Mantoux test.

Interpretation of tuberculin skin tests

According to the U.S. guidelines, latent tuberculosis is diagnosed on a Mantoux test if there is more than 10 (recent immigrant, under age of 4 or have other risk factors for the disease) or 15 mm (no risk factors) of induration. In high risk groups, such as those who are HIV positive, the cut-off is 5 mm on induration. The U.S. guidelines recommend that a history of previous BCG vaccination should be ignored. For details of tuberculin skin test interpretation, please refer to the CDC guidelines (reference given below).

The UK guidelines are formulated according to the Heaf test: In patients who have had BCG previously, latent TB is diagnosed if the Heaf test is grade 3 or 4 and have no signs or symptoms of active TB; if the Heaf test is grade 0 or 1, then the test is repeated and. In patients who have not had BCG previously, latent TB is the Heaf test if grade 2, 3 or 4, and have no signs or symptoms of active TB. Repeat Heaf testing is not done in patients who have had BCG (because of the phenomenon of boosting). For details of tuberculin skin test interpretation, please refer to the BTS guidelines (references given below).

Given that the US recommendation is that prior BCG vaccination be ignored in the interpretation of tuberculin skin tests, false positives are possible as a result of: (1) people who have previously had BCG (even many years ago) may still have a false positive Mantoux test, and (2) serial testing with tuberculin skin tests boosts the immunological response in those people who have previously had BCG, so these people will falsely appear to be tuberculin converters. This may lead to treating more people than necessary, with the possible risk of those patients suffering adverse drug reactions. However, as Bacille Calmette-Guérin vaccine is not 100% effective, and is less protective in adults than pediatric patients, not treating these patients could lead to a possible infection. The current US policy seems to a reflect a desire to err on the side of safety (of the general public).

The U.S. guidelines also allow for tuberculin skin testing in immunosuppressed patients (those with HIV, or who are on immunosuppressive drugs), whereas the UK guidelines recommend that tuberculin skin tests should not be used for such patients because it is unreliable.

γ-interferon testing

The role of gamma interferon tests is under going constant review and various guidelines have been published with the option for revision as new data comes to hand.CDC:MMWR Health Protection Agency:UK

There are currently (26 March 2009) three commercially available interferon-γ release assays (IGRAs): QuantiFERON-TB Gold, QuantiFERON-TB Gold In-Tube and T-SPOT.TB. These tests are not affected by prior BCG vaccination, and look for the body's response to specific TB antigens not present in other forms of mycobacteria and BCG (ESAT-6). Whilst these tests are new they are now becoming available globally.

CDC:

CDC recommends that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for health-care workers).

HPA Interim Guidance:

The HPA recommends the use of IGRA testing in health care workers, if available, in view of the importance of detecting latently infected staff who may go on to develop active disease and come into contact with immunocompromised patients and the logistical simplicity of IGRA testing.

Treatment

The treatment of latent tuberculosis infection (LTBI) is essential to controlling and eliminating TB by reducing the risk that TB infection will progress to disease. The gold standard of treatment is nine months of isoniazid, and this regimen is still widely used in the U.S. (but not elsewhere).

Terminology

There is no agreement regarding terminology: the terms **preventive therapy** and **chemoprophylaxis** have been used for decades, and are preferred in the UK because it involves giving medication to people who have no disease and are currently well: the reason for giving medication is primarily to prevent people from becoming unwell. In the U.S., physicians talk about **latent tuberculosis treatment** because the medication does not actually prevent infection: the person is already infected and the medication prevents existing silent infection from becoming active disease. There are no convincing reasons to prefer one term over the other.

Treatment regimens

It is essential that assessment to rule out active TB be carried out before treatment for LTBI is started. To give treatment for latent tuberculosis to someone with active tuberculosis is a serious error: the tuberculosis will not be adequately treated and there is a serious risk of developing drug-resistant strains of TB.

There are several treatment regimens currently in use:

- 9H — Isoniazid for 9 months is the gold standard (93% effective).
- 6H — Isoniazid for 6 months might be adopted by a local TB program based on cost-effectiveness and patient compliance. This is the regimen currently recommended in the UK for routine use. The U.S. guidance excludes this regimen from use in children or persons with radiographic evidence of prior tuberculosis (old fibrotic lesions) (69% effective).
- 6 to $9H_2$ — An intermittent twice-weekly regimen for the above 2 treatment regimens is an alternative if administered under Directly observed therapy (DOT).
- 4R — Rifampin for 4-months is an alternative for those who are unable to take isoniazid or who have had known exposure to isoniazid-resistant TB.
- 3HR — Isoniazid and rifampin may be given daily for three months.
- 2RZ — The two month regimen of rifampin and pyrazinamide is no longer recommended for treatment of LTBI because of the greatly increased risk of drug-induced hepatitis and death.

Multi-drug-resistant TB

There is no evidence for any regimen used for persons with known exposure to MDR-TB and no consensus on optimal treatment. A regimen consisting of ethambutol and PAS has

been used before. It would appear sensible to choose a combination of antibiotics based on the known sensitivities of the organism. The CDC have recommended a combination of pyrazinamide and ethambutol, with either pyrazinamide or fluoroquinolone. Immunocompetent contacts should be treated for 6 months; immunocompromised contacts should be treated for 12 months.

Research

Although a tuberculosis cure was developed more than 50 years ago, TB continues to kill from 2 to 3 million people every year. According to the World Health Organization (WHO) approximately 36 million people will die of tuberculosis by 2020 if it is not controlled. They add that eight million people develop active tuberculosis every year. Approximately 98 percent of those victims are from developing countries. Furthermore, WHO estimates that approximately one-third of the world's population are carriers of latent tuberculosis.

Therefore, the scientific community continues its research efforts to learn more from this disease in order to develop more options for possible treatments.

The factors that trigger latent tuberculosis infection to progress into active disease have been unknown. However, Professor David Russell and his group at Cornell University in New York, USA, recently demonstrated that the bacteria responsible for causing TB are able to hijack fat metabolism in the host to drive the progression of the disease.

The research made clear that the Mycrobacterium tuberculosis is able to stimulate the immune cells they infect resulting in the accumulation of fat droplets. These droplets turn into what they called “foamy” cells and such transformation can trigger a reawakening of the TB infection from its latent state. Professor Russell believes that more knowledge about the bacterium's life cycle and its host interactions will open possibilities to develop new treatments.

Another group of researchers at Sydney's Centenary Institute made an important discovery that could lead to the development of a new drug for TB. The team, led by Dr Nick West, investigated a protein that is essential for TB to survive and later they reported some success in developing a drug that would inhibit this protein. If the group is successful in finding a way to treat latent tuberculosis, millions of people around the world could be saved.

Furthermore, researchers from the Genome Institute of Singapore together with collaborators in The Netherlands, Indonesia, United Kingdom, and the Russian Federation, identified a new gene that would provide susceptibility to pulmonary tuberculosis. The gene is named Toll-like receptor 8 (TLR8) and it recognizes some factors from viruses such as HIV. This gene is believed to also have a role in human susceptibility to Mycobacterium tuberculosis infections. This discovery could open new options for therapeutic interventions.

Chapter 5

Tuberculosis Diagnosis

Tuberculosis is diagnosed by finding *Mycobacterium tuberculosis* bacteria in a clinical specimen taken from the patient. While other investigations may strongly suggest tuberculosis as the diagnosis, they cannot confirm it.

Diagnosis

A complete medical evaluation for tuberculosis (TB) must include a medical history, a physical examination, a chest X-ray and microbiological examination (of sputum or some other appropriate sample). It may also include a tuberculin skin test, other scans and X-rays, surgical biopsy.

Medical history

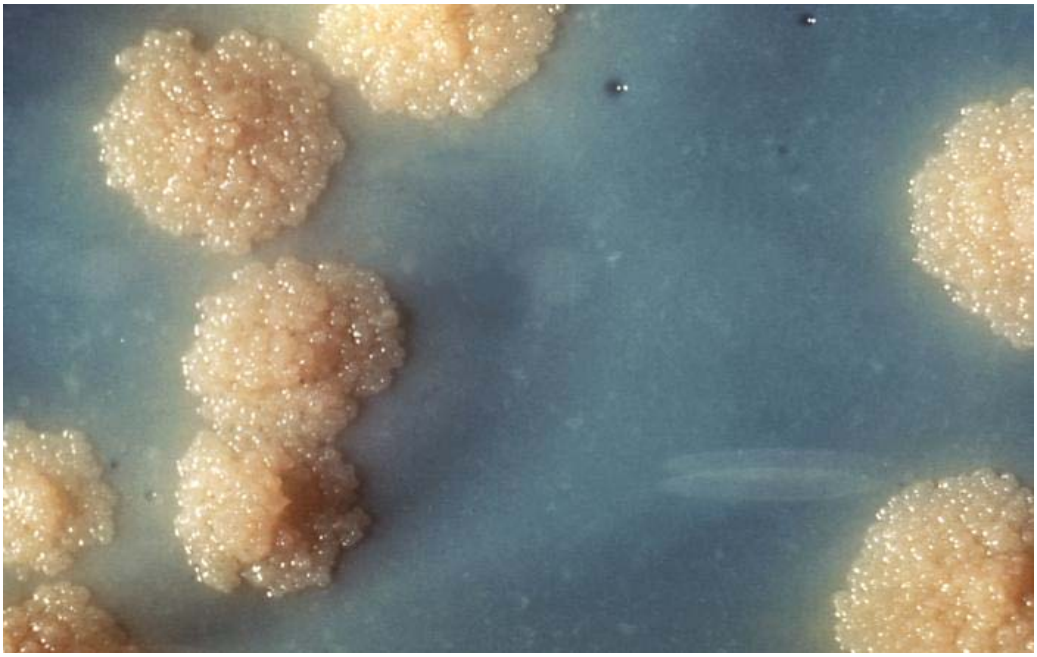
The medical history includes obtaining the symptoms of pulmonary TB: productive, prolonged cough of three or more weeks, chest pain, and hemoptysis. Systemic symptoms include low grade remittent fever, chills, night sweats, appetite loss, weight loss, easy fatiguability, and production of sputum that starts out mucoid but changes to purulent. Other parts of the medical history include prior TB exposure, infection or disease; past TB treatment; demographic risk factors for TB; and medical conditions that increase risk for TB disease such as HIV infection.

Tuberculosis should be suspected when a persistent respiratory illness in an otherwise healthy individual does not respond to regular antibiotics.

Physical examination

A physical examination is done to assess the patient's general health and find other factors which may affect the TB treatment plan. It cannot be used to confirm or rule out TB.

Microbiological studies



Distinctive clusters of colorless *Mycobacterium tuberculosis* form in this culture

A definitive diagnosis of tuberculosis can only be made by culturing *Mycobacterium tuberculosis* organisms from a specimen taken from the patient (most often sputum, but may also include pus, CSF, biopsied tissue, etc.). A diagnosis made other than by culture may only be classified as "probable" or "presumed". For a diagnosis negating the possibility of tuberculosis infection, most protocols require that two separate cultures both test negative.

Sputum

Sputum smears and cultures should be done for acid-fast bacilli if the patient is producing sputum. The preferred method for this is fluorescence microscopy (auramine-rhodamine staining), which is more sensitive than conventional Ziehl-Neelsen staining. In cases where there is no spontaneous sputum production, a sample can be induced, usually by nebulized inhalation of a saline or saline with bronchodilator solution. A comparative study found that inducing three sputum samples is more sensitive than three gastric washings.

Alternative sampling

In patients incapable of producing a sputum sample, common alternative sample sources for diagnosing pulmonary tuberculosis include gastric washings, laryngeal swab, bronchoscopy (with bronchoalveolar lavage, bronchial washings, and/or transbronchial biopsy), and fine needle aspiration (transtracheal or transbronchial). In some cases, a

more invasive technique is necessary, including tissue biopsy during mediastinoscopy or thoracoscopy.

PCR

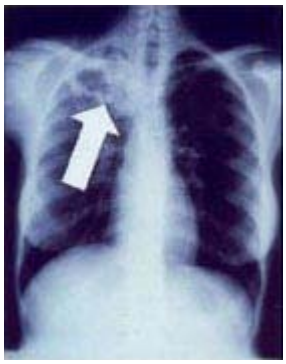
Other mycobacteria are also acid-fast. If the smear is positive, PCR or gene probe tests can distinguish *M. tuberculosis* from other mycobacteria. Even if sputum smear is negative, tuberculosis must be considered and is only excluded after negative cultures.

Other

Many types of cultures are available . Traditionally, cultures have used the Löwenstein-Jensen (LJ), Kirchner, or Middlebrook media (7H9, 7H10, and 7H11). A culture of the AFB can distinguish the various forms of mycobacteria, although results from this may take four to eight weeks for a conclusive answer. New automated systems that are faster include the MB/BacT, BACTEC 9000, and the Mycobacterial Growth Indicator Tube (MGIT). The Microscopic Observation Drug Susceptibility assay culture may be a faster and more accurate method .

Radiography

Chest X-ray



Tuberculosis creates cavities visible in x-rays like this one in the patient's right upper lobe.

In active pulmonary TB, infiltrates or consolidations and/or cavities are often seen in the upper lungs with or without mediastinal or hilar lymphadenopathy or pleural effusions (tuberculous pleurisy). However, lesions may appear anywhere in the lungs. In disseminated TB a pattern of many tiny nodules throughout the lung fields is common - the so called miliary TB. In HIV and other immunosuppressed persons, any abnormality may indicate TB or the chest X-ray may even appear entirely normal.

Abnormalities on chest radiographs may be suggestive of, but are never diagnostic of, TB. However, chest radiographs may be used to rule out the possibility of pulmonary TB

in a person who has a positive reaction to the tuberculin skin test and no symptoms of disease.

Cavitation or consolidation of the apexes of the upper lobes of the lung may be discernible by a chest x-ray .

Abreugraphy

A variant of the chest X-Ray, abreugraphy (from the name of its inventor, Dr. Manuel Dias de Abreu) was a small radiographic image, also called miniature mass radiography (MMR) or miniature chest radiograph. Though its resolution is limited (it doesn't allow the diagnosis of lung cancer, for example) it is sufficiently accurate for diagnosis of tuberculosis.

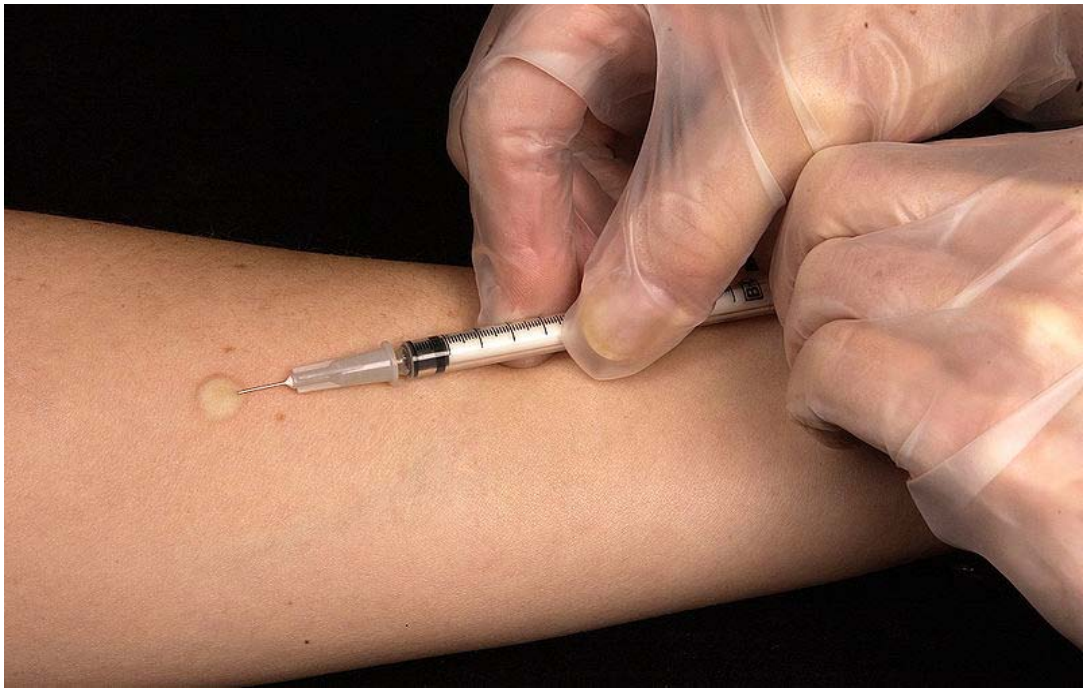
Much less expensive than traditional X-Ray, MMR was quickly adopted and extensively utilized in some countries, in the 1950s. For example, in Brazil and in Japan, tuberculosis prevention laws went into effect, obligating ca. 60% of the population to undergo MMR screening.

The procedure went out of favor, as the incidence of tuberculosis dramatically decreased, but is still used in certain situations, such as the screening of prisoners and immigration applicants..

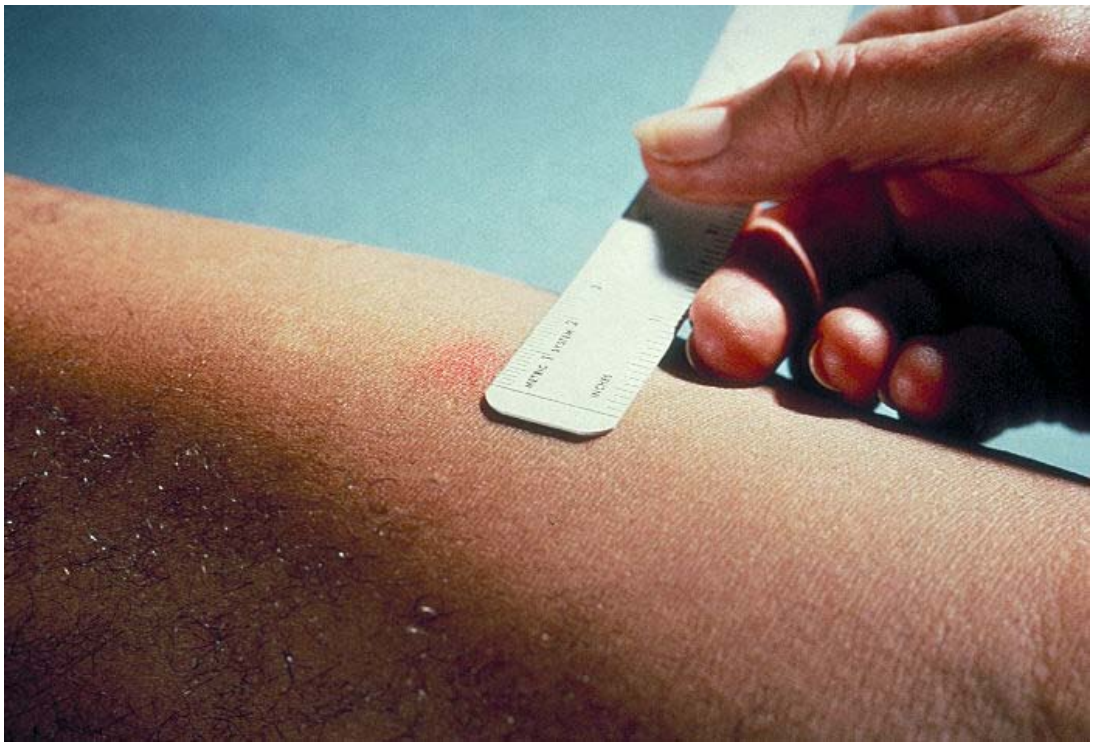
Tuberculin skin test (TST)

Two tests are available: the Mantoux and Heaf tests.

Mantoux skin test



Injecting a Mantoux skin test



The Mantoux test for TB involves intradermally injecting PPD (Purified Protein Derivative) tuberculin and measuring the size of induration 48-72 hours later.

The Mantoux skin test is used in the United States and is endorsed by the American Thoracic Society and Centers for Disease Control and Prevention (CDC).

If a person has had a history of a positive tuberculin skin test, another skin test is not needed.

Heaf test

The Heaf test was used in the United Kingdom until 2005, and is graded on a four point scale. The Mantoux test is now used.

The equivalent Mantoux test positive levels done with 10 TU (0.1 ml 100 TU/ml, 1:1000) are

- 0–4 mm induration (Heaf 0 to 1)
- 5–14 mm induration (Heaf 2)
- Greater than 15 mm induration (Heaf 3 to 5)

CDC classification of tuberculin reaction

An induration (palpable raised hardened area of skin) of more than 5–15 mm (depending upon the person's risk factors) to 10 Mantoux units is considered a positive result, indicating TB infection.

- 5 mm or more is positive in
  - HIV-positive person
  - Recent contacts of TB case
  - Persons with nodular or fibrotic changes on CXR consistent with old healed TB
  - Patients with organ transplants and other immunosuppressed patients

- 10 mm or more is positive in
  - Recent arrivals (less than 5 years) from high-prevalent countries
  - Injection drug users
  - Residents and employees of high-risk congregate settings (e.g., prisons, nursing homes, hospitals, homeless shelters, etc.)
  - Mycobacteriology lab personnel
  - Persons with clinical conditions that place them at high risk (e.g., diabetes, prolonged corticosteroid therapy, leukemia, end-stage renal disease, chronic malabsorption syndromes, low body weight, etc)
  - Children less than 4 years of age, or children and adolescents exposed to adults in high-risk categories

- 15 mm or more is positive in
  - Persons with no known risk factors for TB

- (Note: Targeted skin testing programs should only be conducted among high-risk groups)

A tuberculin test conversion is defined as an increase of 10 mm or more within a 2-year period, regardless of age.

BCG vaccine and tuberculin skin test

There is disagreement on the use of the Mantoux test on people who have been immunized with BCG. The US recommendation is that in administering and interpreting the Mantoux test, previous BCG vaccination should be ignored; the UK recommendation is that interferon-γ tests should be used to help interpret positive tuberculin tests, also, the UK do not recommend serial tuberculin skin testing in people who have had BCG (a key part of the US strategy). In their guidelines on the use of QuantiFERON Gold the US Centers for Disease Control and Prevention state that whereas Quantiferon Gold is not affected by BCG inoculation tuberculin tests can be affected. In general the US approach is likely to result in more false positives and more unnecessary treatment with potentially toxic drugs; the UK approach is as sensitive in theory and should also be more specific, because of the use of interferon-γ tests.

Under the US recommendations, diagnosis and treatment of latent tuberculosis infection (LTBI) is considered for any BCG-vaccinated person whose skin test is 10 mm or greater, if any of these circumstances are present:

- Was in contact with another person with infectious TB
- Was born or has resided in a high TB prevalence country
- Is continually exposed to populations where TB prevalence is high.

Laboratory

Because of difficulties with the Tuberculin skin test, many laboratory methods of diagnosis are emerging. These tests have been reviewed in detail .

Adenosine deaminase

In 2007, a systematic review of adenosine deaminase by the NHS Health Technology Assessment Programme concluded "There is no evidence to support the use of ADA tests for the diagnosis of pulmonary TB. However, there is considerable evidence to support their use in pleural fluid samples for diagnosis of pleural TB, where sensitivity was very high, and to a slightly lesser extent for TB meningitis. In both pleural TB and TB meningitis, ADA tests had higher sensitivity than any other tests."

Nucleic acid amplification tests (NAAT)

This is a heterogeneous group of tests that use the polymerase chain reaction (PCR) technique to detect mycobacterial nucleic acid. These test vary in which nucleic acid

sequence they detect and vary in their accuracy. The two most common commercially available tests are the amplified mycobacterium tuberculosis direct test (MTD, Gen-Probe) and Amplicor (Roche Diagnostics). In 2007, a systematic review of NAAT by the NHS Health Technology Assessment Programme concluded that "NAAT test accuracy to be far superior when applied to respiratory samples as opposed to other specimens. Although the results were not statistically significant, the AMTD test appears to perform better than other currently available commercial tests."

In a more recent before-after observational study, found that use of the MTD test reduce inappropriate tuberculosis therapy. The study found the accuracy of the MTD test as follows:

Overall

- sensitivity 92%
- specificity 99%

Smear positive patients

- sensitivity 99%
- specificity 98%

Smear negative patients

- sensitivity 62%
- specificity 99%

Full blood count

Although a full blood count is never diagnostic, normocytic anemia and lymphopenia are common. Neutrophilia is rarely found. [iron deficiency anemia may develop with isoniazid treatment] Urea and electrolytes are usually normal, although hypocalcemia and hyponatremia are possible in tuberculous meningoencephalitis due to SIADH. In advanced disease, hypoalbuminemia, hyperproteinemia, and hyperglobulinemia may be present.

Erythrocyte sedimentation rate is usually raised.

Interferon-γ release assays

Interferon-γ (interferon-gamma) release assays (IGRAs) are exciting new developments in TB infection testing. IGRAs are based on the ability of the *Mycobacterium tuberculosis* antigens for early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) to stimulate host production of interferon-gamma. Because these antigens are not present in non-tuberculous mycobacteria or in any BCG vaccine variant, these tests can distinguish latent tuberculosis infection (LTBI).

The blood tests QuantiFERON-TB Gold In Tube and T-SPOT.TB use these antigens to detect people with tuberculosis. Lymphocytes from the patient's blood are incubated with the antigens. These tests are called interferon γ tests and are not equivalent. If the patient has been exposed to tuberculosis before, T lymphocytes produce interferon γ in response. The QuantiFERON-TB Gold In Tube uses an ELISA format to detect the whole blood production of interferon γ with great sensitivity (89%). The distinction between the tests is that QuantiFERON-TB Gold quantifies the total amount of interferon γ when whole blood is exposed to the antigens(ESAT-6,CFP-10 and TB 7.7(p4)), whereas Guidelines for the use of the FDA approved QuantiFERON-TB Gold were released by the CDC in December 2005. In October 2007, the FDA gave approval of QuantiFERON-TB Gold In Tube for use in the United States.

The enzyme-linked immunospot assay (ELISPOT) is another blood test available in the UK that may replace the skin test for diagnosis . T-SPOT.TB, a type of ELISPOT assay, counts the number of activated T lymphocytes that secrete interferon γ.

For diagnosing *latent* TB, three systematic reviews of IGRAs concluded the tests noted excellent specificity for the tests to distinguish latent TB from prior vaccination.

According to a study from Korea, where there is a high prevalence of LTBI, QuantiFERON-TB Gold and T-SPOT.TB have good sensitivity but reduced specificity for diagnosing *active* TB, due to their ability to detect latent TB. In a recently published metaanalysis , with data from both developed and developing countries, QuantiFERON-TB Gold In Tube had a pooled sensitivity for active TB of 81% and specificity of 99.2%, whereas T-SPOT.TB had a pooled sensitivity of 87.5% and specificity of 86.3%. In head-to-head comparisons, the sensitivity of IGRAs surpassed TST. The authors concluded that IGRAs are "superior to the TST for detecting confirmed active TB disease..."

Public health

When someone is diagnosed with tuberculosis, all their close contacts should be screened for TB with a tuberculin skin test or a chest x-ray or both.

Tuberculosis classification system used in the US

The current clinical classification system for TB (Class 0 to 5) is based on the pathogenesis of the disease.

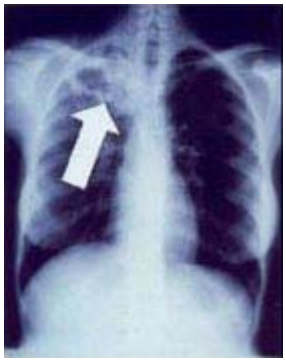
The U.S. Citizenship and Immigration Services has an additional TB classification (Class A, B1, or B2) for immigrants and refugees developed by the Centers for Disease Control and Prevention (CDC). The (Class) *B notification program* is an important screening strategy to identify new arrivals who have a high risk for TB.

Chapter 6

Tuberculosis Radiology

Radiology is used in the diagnosis of tuberculosis.

Chest X-ray



Tuberculosis creates cavities visible in x-rays like this one in the patient's right upper lobe.

A posterior-anterior (PA) chest X-ray is the standard view used; other views (lateral or lordotic) or CT scans may be necessary.

In active pulmonary TB, infiltrates or consolidations and/or cavities are often seen in the upper lungs with or without mediastinal or hilar lymphadenopathy. However, lesions may appear anywhere in the lungs. In HIV and other immunosuppressed persons, any abnormality may indicate TB or the chest X-ray may even appear entirely normal.

Old healed tuberculosis usually presents as pulmonary nodules in the hilar area or upper lobes, with or without fibrotic scars and volume loss. Bronchiectasis and pleural scarring may be present.

Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with the potential for future progression to active tuberculosis. Persons with these findings, if they have a positive tuberculin skin test reaction, should be considered high-priority candidates for treatment of latent infection regardless of age. Conversely, calcified nodular lesions (calcified granuloma) pose a very low risk for future progression to active tuberculosis.

Abnormalities on chest radiographs may be suggestive of, but are never diagnostic of, TB. However, chest radiographs may be used to rule out the possibility of pulmonary TB in a person who has a positive reaction to the tuberculin skin test and no symptoms of disease.

CDC guidelines for evaluating CXR

A medical examination is mandatory for all refugees coming to the U.S. and all applicants outside the U.S. applying for an immigrant visa. The purpose of the medical examination is to identify applicants with inadmissible health-related conditions such as active tuberculosis. Outside the U.S., medical examinations are performed by approximately 400 physicians (panel physicians) selected by United States Department of State consular officials. In the U.S., medical examinations are performed by approximately 3,000 physicians (civil surgeons) designated by district directors of the U.S. Citizenship and Immigration Services. Guidelines were developed by the Centers for Disease Control and Prevention (CDC).

The chest X-ray and classification worksheet is designed to group findings into categories based on their likelihood of being related to TB or non-TB conditions needing medical follow-up (either at the time of the chest X-ray or after resettlement).

Normal findings

These are films that are completely normal, with no identifiable cardiothoracic or musculoskeletal abnormality.aa or

Abnormal findings

Chest X-Ray Findings that Can Suggest ACTIVE TB

This category comprises all findings typically associated with active pulmonary TB. An applicant with any of the following findings must submit sputum specimens for examination.

1. Infiltrate or consolidation - Opacification of airspaces within the lung parenchyma. Consolidation or infiltrate can be dense or patchy and might have irregular, ill-defined, or hazy borders.
2. Any cavitary lesion - Lucency (darkened area) within the lung parenchyma, with or without irregular margins that might be surrounded by an area of airspace consolidation or infiltrates, or by nodular or fibrotic (reticular) densities, or both. The walls surrounding the lucent area can be thick or thin. Calcification can exist around a cavity.
3. Nodule with poorly defined margins - Round density within the lung parenchyma, also called a tuberculoma. Nodules included in this category are those with margins that are indistinct or poorly defined. The surrounding haziness can be either subtle or readily apparent and suggests coexisting airspace consolidation.

4. Pleural effusion - Presence of a significant amount of fluid within the pleural space. This finding must be distinguished from blunting of the costophrenic angle, which may or may not represent a small amount of fluid within the pleural space (except in children when even minor blunting must be considered a finding that can suggest active TB).
5. Hilar or mediastinal lymphadenopathy (bihilar lymphadenopathy) - Enlargement of lymph nodes in one or both hila or within the mediastinum, with or without associated atelectasis or consolidation.
6. Linear, interstitial disease (in children only) - Prominence of linear, interstitial (septal) markings.
7. Other - Any other finding suggestive of active TB, such as miliary TB. Miliary findings are nodules of millet size (1 to 2 millimeters) distributed throughout the parenchyma.

Chest X-Ray Findings that Can Suggest INACTIVE TB

This category includes findings that are suggestive of prior TB, that is inactive. It must be remembered that assessments of the activity of TB cannot be made accurately on the basis of a single radiograph alone. If there is any question of active TB, sputum smears must be obtained. Therefore, any applicant might have findings grouped in this category, but still have active TB as suggested by

- The presence of signs or symptoms of TB (Class B1).
- Sputum smears positive for AFB (Class A).

1. Discrete fibrotic scar or linear opacity—Discrete linear or reticular densities within the lung. The edges of these densities should be distinct and there should be no suggestion of airspace opacification or haziness between or surrounding these densities. Calcification can be present within the lesion and then the lesion is called a “fibrocalcific” scar.
2. Discrete nodule(s) without calcification—One or more nodular densities with distinct borders and without any surrounding airspace opacification. Nodules are generally round or have rounded edges. These features allow them to be distinguished from infiltrates or airspace opacities. To be included here, these nodules must be noncalcified. Nodules that are calcified are included in the category “OTHER X-ray findings, No follow-up needed”.
3. Discrete fibrotic scar with volume loss or retraction—Discrete linear densities with reduction in the space occupied by the upper lobe. Associated signs include upward deviation of the fissure or hilum on the corresponding side with asymmetry of the volumes of the two thoracic cavities.
4. Discrete nodule(s) with volume loss or retraction—One or more nodular densities with distinct borders and no surrounding airspace opacification with reduction in the space occupied by the upper lobe. Nodules are generally round or have rounded edges.

5. Other—Any other finding suggestive of prior TB, such as upper lobe bronchiectasis. Bronchiectasis is bronchial dilation with bronchial wall thickening.

OTHER Chest X-Ray Findings

Follow-up needed

This category includes findings that suggest the need for a follow-up evaluation for non-TB conditions either at the time of the chest X-ray or after resettlement of the applicant in the United States.

1. Musculoskeletal abnormalities - New bony fractures or radiographically apparent bony abnormalities that need follow-up.
2. Cardiac abnormalities - Cardiac enlargement or anomalies, vascular abnormalities, or any other radiographically apparent cardiovascular abnormality of significant nature to require follow-up.
3. Pulmonary abnormalities - Pulmonary finding of a non-TB nature, such as a mass, that needs follow-up.
4. Other - Any other finding that the panel physician believes needs follow-up, but is not one of the above.

No follow-up needed

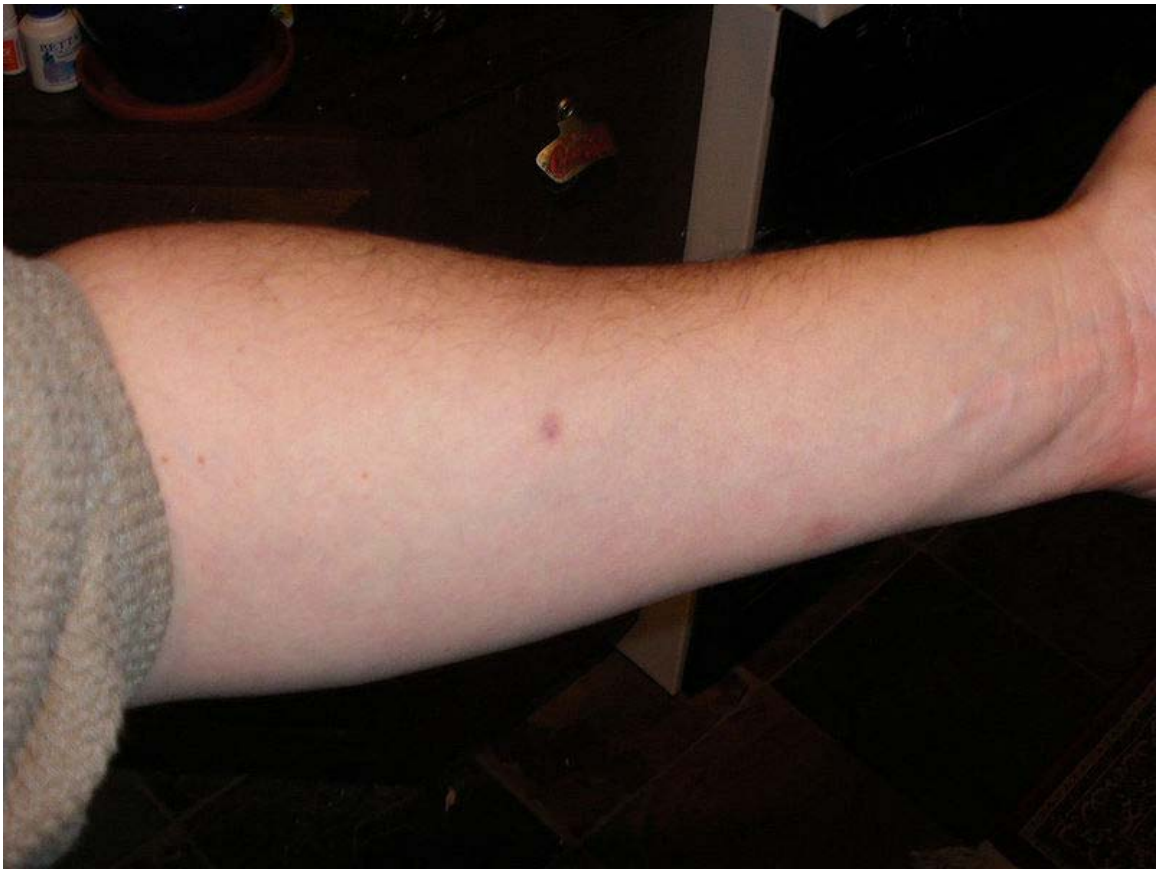
This category includes findings that are minor and not suggestive of TB disease. These findings require no follow-up evaluation after resettlement of the applicant.

1. Pleural thickening - Irregularity or abnormal prominence of the pleural margin, including apical capping (thickening of the pleura in the apical region). Pleural thickening can be calcified.
2. Diaphragmatic tenting - A localized accentuation of the normal convexity of the hemidiaphragm as if "pulled upwards by a string."
3. Blunting of costophrenic angle (in adults)—Loss of sharpness of one or both costophrenic angles. Blunting can be related to a small amount of fluid in the pleural space or to pleural thickening and, by itself, is a non-specific finding (except in children, when even minor blunting may suggest active TB). In contrast a large pleural effusion, or the presence of a significant amount of fluid in the pleural space, may be a sign of active TB at any age.
4. Solitary calcified nodules or granuloma - Discrete calcified nodule or granuloma, or calcified lymph node. The calcified nodule can be within the lung, hila, or mediastinum. The borders must be sharp, distinct, and well defined. This was considered a Class B3 TB in the past; however, Class B3 has been omitted from the classification scheme because it has not been found to be associated with active TB.
5. Minor musculoskeletal findings - Minor findings needing no follow-up.
6. Minor cardiac findings - Minor findings needing no follow-up.

Chapter 7

Mantoux Test and Chest Photofluorography

Mantoux test



Mantoux test injection site in a subject without chronic conditions or in a high risk group clinically diagnosed as negative at 50 hours.

The **Mantoux test** (also known as the **Mantoux screening test**, **Tuberculin Sensitivity Test**, **Pirquet test**, or **PPD test** for Purified Protein Derivative) is a diagnostic tool for

tuberculosis. It is one of the two major tuberculin skin tests used in the world, largely replacing multiple-puncture tests such as the Tine test. Until 2005, the Heaf test was used in the United Kingdom, but the Mantoux test is now used. The Mantoux test is also used in Australia, Brazil, Canada, Hungary, Poland, Russia, India, Netherlands, New Zealand, Spain, Portugal, South Africa and the United States and is endorsed by the American Thoracic Society and Centers for Disease Control and Prevention (CDC)). It was also used in the USSR and is now prevalent in most of the former Soviet states.

History

Tuberculin is a glycerol extract of the tubercle bacillus. Purified protein derivative (PPD) tuberculin is a precipitate of non-species-specific molecules obtained from filtrates of sterilized, concentrated cultures. It was first described by Robert Koch in 1890. The test is named after Charles Mantoux, a French physician who developed on the work of Koch and Clemens von Pirquet to create his test in 1907.

In 1939, M. A. Linnikova in the USSR created a modified version of PPD. In 1954, the Soviet Union started mass production of PPD-L, named after Linnikova.

Procedure

A standard dose of 5 Tuberculin units (0.1 mL) (The standard Mantoux test in the UK consists of an intradermal injection of 2TU of Statens Serum Institute (SSI) tuberculin RT23 in 0.1ml solution for injection.) is injected intradermally (between the layers of dermis) and read 48 to 72 hours later. This intradermal injection is termed the **mantoux technique**. A person who has been exposed to the bacteria is expected to mount an immune response in the skin containing the bacterial proteins.

The reaction is read by measuring the diameter of induration (palpable raised hardened area) across the forearm (perpendicular to the long axis) in millimeters. If there is no induration, the result should be recorded as "0 mm". Erythema (redness) should not be measured.

If a person has had a history of a positive tuberculin skin test, or has not had a recent tuberculin skin test (within one year), another skin test may be needed.

Classification of tuberculin reaction

The results of this test must be interpreted carefully. The person's medical risk factors determine at which increment (5 mm, 10 mm, or 15 mm) of induration the result is considered positive. A positive result indicates TB exposure.

- 5 mm or more is positive in
    - HIV-positive person
    - Recent contacts of TB case

    - Persons with nodular or fibrotic changes on chest x-ray consistent with old healed TB
    - Patients with organ transplants and other immunosuppressed patients
- 10 mm or more is positive in
    - Recent arrivals (less than 5 years) from high-prevalence countries
    - Injection drug users
    - Residents and employees of high-risk congregate settings (e.g., prisons, nursing homes, hospitals, homeless shelters, etc.)
    - Mycobacteriology lab personnel
    - Persons with clinical conditions that place them at high risk (e.g., diabetes, prolonged corticosteroid therapy, leukemia, end-stage renal disease, chronic malabsorption syndromes, low body weight, etc.)
    - Children less than 4 years of age, or children and adolescents exposed to adults in high-risk categories
- 15 mm or more is positive in
    - Persons with no known risk factors for TB
    - (Note: Targeted skin testing programs should only be conducted among high-risk groups)

A tuberculin test conversion is defined as an increase of 10 mm or more within a 2-year period, regardless of age.

False positive result

Due to the test's low specificity, most positive reactions in low-risk individuals are false-positives. A false positive result may be caused by nontuberculous mycobacteria or previous administration of BCG vaccine. Prior vaccination with BCG may result in a false-positive result for many years afterwards.

False positives can also occur when the injected area is touched, causing swelling and itching.

False negative result

Those that are immunologically compromised, especially those with HIV and low CD4 T cell counts, frequently show negative results from the PPD test. This is because the immune system needs to be functional to mount a response to the protein derivative injected under the skin.

BCG vaccine and the Mantoux test

There is disagreement about the role of Mantoux testing in people who have been vaccinated. The US recommendation is that tuberculin skin testing is not contraindicated for BCG-vaccinated persons and that prior BCG vaccination should not influence the interpretation of the test. The UK recommendation is that interferon-γ testing should be used to help interpret positive Mantoux tests, and that serial tuberculin skin testing must

not be done in people who have had prior BCG vaccination. In general, the US recommendation results in a much larger number of people being falsely diagnosed with latent tuberculosis, while the UK approach probably misses patients with latent tuberculosis who should be treated.

According to the U. S. guidelines, latent tuberculosis infection (LTBI) diagnosis and treatment for LTBI is considered for any BCG-vaccinated person whose skin test is 10 mm or greater, if any of these circumstances are present:

- Was in contact with another person with infectious TB
- Was born or has lived in a high TB prevalence country
- Is continually exposed to populations where TB prevalence is high.

Anergy testing

In cases of anergy, a lack of reaction by the body's defence mechanisms when it comes into contact with foreign substances, the tuberculin reaction will occur weakly, thus compromising the value of Mantoux testing. For example, anergy is present in AIDS, a disease which strongly depresses the immune system. Therefore, anergy testing is advised in cases where suspicion is warranted that it is present. However, routine anergy skin testing is not recommended.

Two-step testing

Some people who were previously infected with TB may have a negative reaction when tested years after infection, as the immune system response may gradually wane. This initial skin test, though negative, may stimulate (boost) the body's ability to react to tuberculin in future tests. Thus, a positive reaction to a subsequent test may be misinterpreted as a new infection, when in fact it is the result of the boosted reaction to an old infection.

Use two-step testing for **initial** skin testing of adults who will be retested periodically (e.g., health care workers). This ensures that any future positive tests can be interpreted as being caused by a new infection, rather than simply a reaction to an old infection.

- Return to have first test read 48–72 hours after injection
- If first test is positive, consider the person infected.
- If first test is negative, give second test 1–3 weeks after first injection
- Return to have second test read 48–72 hours after injection
- If second test is positive, consider person previously infected
- If second test is negative, consider person uninfected

A person who is diagnosed as "infected" on two-step testing is called a "tuberculin converter". The US recommendation that prior BCG-vaccination be ignored results in almost universal false diagnosis of tuberculosis infection in people who have had BCG (mostly foreign nationals).

Recent developments

As a replacement for the Mantoux test, several other tests are being developed. QuantiFERON-TB Gold is a blood test that measures the patient's immune reactivity to the TB bacterium and is useful for initial and serial testing of persons with an increased risk of latent or active tuberculosis infection. Guidelines for the use of the QuantiFERON test were released by the CDC in December 2005. QuantiFERON-TB Gold is Food and Drug Administration (FDA) approved in the United States, has CE Mark approval in Europe and has been approved by the MHLW in Japan.

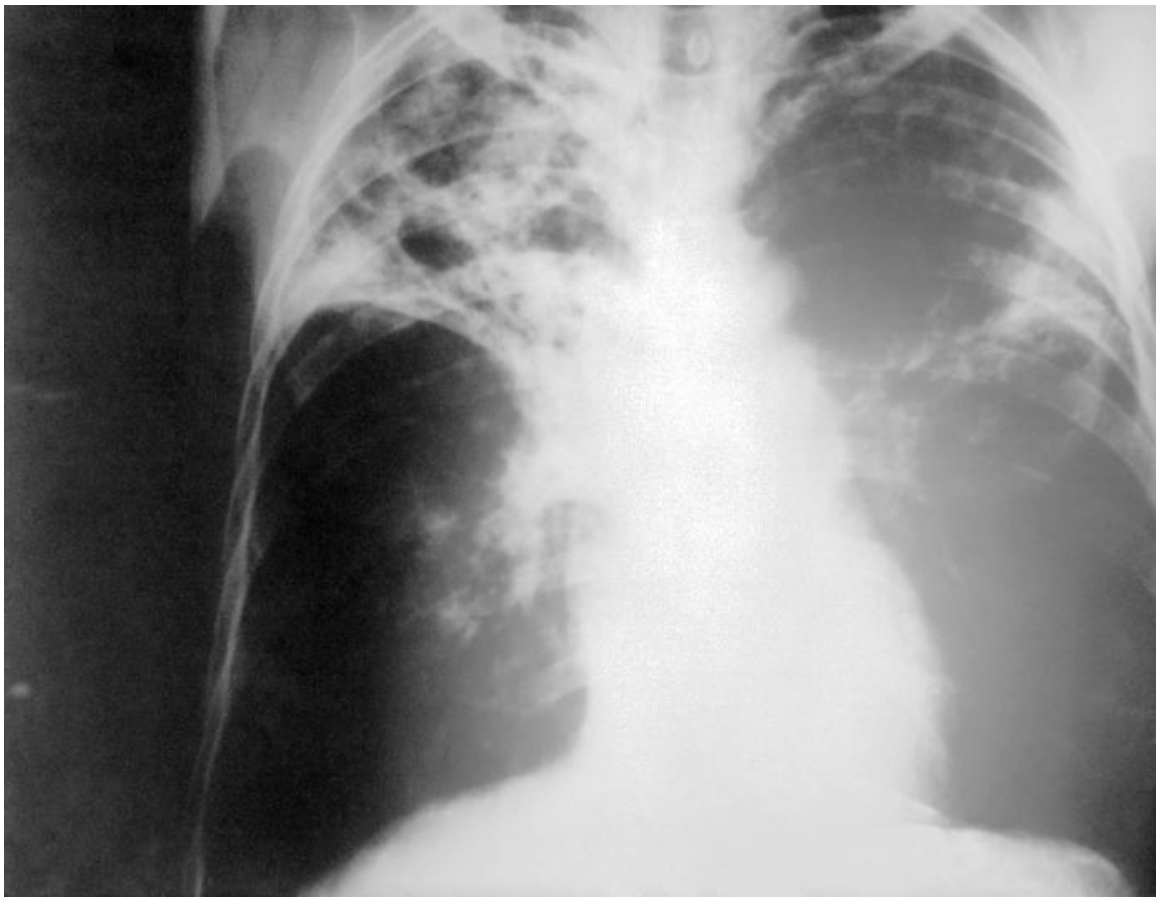
Heaf test

The Heaf test is a tuberculin skin test formerly used in the United Kingdom, but discontinued in 2005.

The equivalent Mantoux test positive levels done with 10 TU (0.1 mL 100 TU/mL, 1:1000) are

- <5 mm induration (Heaf 0-1)
- 5–15 mm induration (Heaf 2)
- >15 mm induration (Heaf 3-4)

Chest photofluorography



Chest radiography showing advanced bilateral pulmonary tuberculosis. Source: CDC

Chest photofluorography, or **abreugraphy** (also called **mass miniature radiography**) is a photofluorography technique for mass screening for tuberculosis using a miniature (50 to 100 mm) photograph of the screen of a x-ray fluoroscopy of the thorax, first developed in 1935.

History

Abreugraphy receives its name from its inventor, Dr. Manuel Dias de Abreu, a Brazilian physician and pulmonologist. It has received several different names, according to the country where it was adopted: mass radiography, miniature chest radiograph (United Kingdom and USA), roentgenfluorography (Germany), radiophotography (France), schermografia (Italy), photoradioscopy (Spain) and photofluorography (Sweden).

In many countries, miniature mass radiographs (MMR) was quickly adopted and extensively utilized in the 1950s. For example, in Brazil and in Japan, tuberculosis prevention laws went into effect, obligating ca. 60% of the population to undergo MMR

screening. However, as a mass screening program for low-risk populations, the procedure was largely discontinued in the 1970s, following recommendation of the World Health Organization, due to three main reasons:

1. The dramatic decrease of the general incidence of tuberculosis in developed countries (from 150 cases per 100,000 inhabitants in 1900, 70/100,000 in 1940 and 5/100,000 in 1950);
2. Decreased benefits/cost ratio (a recent Canadian study has shown a cost of CD$ 236,496 per case in groups of immigrants with a low risk for tuberculosis, versus CD$ 3,943 per case in high risk groups);
3. Risk of exposure to ionizing radiation doses, particularly among children, in the presence of extremely low yield rates of detection.

Current use

Mobile Chest photofluorography car in Almaty, Kazakhstan

MMR is still an easy and useful way to prevent transmission of the disease in certain situations, such as in prisons and for immigration applicants and foreign workers coming from countries with a higher risk for tuberculosis. Currently, 13 of the 26 European countries use MMR as the primary screening tool for this purpose. Examples of countries with permanent programs are Italy, Switzerland, Norway, Netherlands, Japan and the United Kingdom.

For example, a study in Switzerland between 1988 and 1990, employing abreugraphy to detect tuberculosis in 50,784 immigrants entering the canton of Vaud, discovered 674 foreign people with abnormalities. Of these, 256 had tuberculosis as the primary diagnosis and 34 were smear or culture-positive (5% of all radiological abnormalities).

Elderly populations are also a good target for MMR-based screening, because the radiation risk is less important and because they have a higher risk of tuberculosis (85 per 100,000 in developed countries, in the average). In Japan, for example, it is still used

routinely, and the Japan Anti-Tuberculosis Association (JATA) reported the detection of 228 cases in 965,440 chest radiographs in 1996 alone.

MMR is most useful at detecting tuberculosis infection in the asymptomatic phase, and it should be combined with tuberculin skin tests and clinical questioning in order to be more effective. The sharp increase in tuberculosis in all countries with large exposure to HIV is probably mandating a return of MMR as a screening tool focusing on high-risk populations, such as homosexuals and intravenous drug users. New advances in digital radiography, coupled with much lower x-ray dosages may herald better MMR technologies.

Chapter 8

Asthma

Asthma (from the Greek άσθμα, *ásthma*, "panting") is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. Symptoms include wheezing, coughing, chest tightness, and shortness of breath.

Treatment of acute symptoms is usually with an inhaled short-acting beta-2 agonist (such as salbutamol). Symptoms can be prevented by avoiding triggers, such as allergens and irritants, and by inhaling corticosteroids. Leukotriene antagonists are less effective than corticosteroids and thus less preferred.

The prevalence of asthma has increased significantly since the 1970s. As of 2009, 300 million people were affected worldwide. In 2009 asthma caused 250,000 deaths globally. Despite this, with proper control of asthma with step down therapy, prognosis is generally good.

Classification

Clinical classification of severity

Severity in patients ≥ 12 years of age	Symptom frequency	Nighttime symptoms	%FEV_1 of predicted	FEV_1 Variability	Use of short-acting $beta_2$ agonist for symptom control (not for prevention of EIB)
Intermittent	≤2 per week	≤2 per month	≥80%	<20%	≤2 days per week
Mild persistent	>2 per week but not daily	3-4 per month	≥80%	20–30%	>2 days/week but not daily
Moderate persistent	Daily	>1 per week but not nightly	60–80%	>30%	Daily
Severe persistent	Throughout the day	Frequent (often 7x/week)	<60%	>30%	Several times per day

Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEV_1), and peak expiratory flow rate. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic), based on whether symptoms are precipitated by allergens (atopic) or not (non-atopic).

While asthma is classified based on severity, at the moment there is no clear method for classifying different subgroups of asthma beyond this system. Within the classifications described above, although the cases of asthma respond to the same treatment differs, thus it is clear that the cases within a classification have significant differences. Finding ways to identify subgroups that respond well to different types of treatments is a current critical goal of asthma research.

Although asthma is a chronic obstructive condition, it is not considered as a part of chronic obstructive pulmonary disease as this term refers specifically to combinations of disease that are irreversible such as bronchiectasis, chronic bronchitis, and emphysema.

Unlike these diseases, the airway obstruction in asthma is usually reversible; however, if left untreated, the chronic inflammation of the lungs during asthma can become irreversible obstruction due to airway remodeling. In contrast to emphysema, asthma affects the bronchi, not the alveoli.

Brittle asthma

Brittle asthma is a term used to describe two types of asthma, distinguishable by recurrent, severe attacks. Type 1 brittle asthma refers to disease with wide peak flow variability, despite intense medication. Type 2 brittle asthma describes background well-controlled asthma, with sudden severe exacerbations.

Asthma attack

An acute asthma exacerbation is commonly referred to as an *asthma attack*. The classic symptoms are shortness of breath, wheezing, and chest tightness. While these are the primary symptoms of asthma, some people present primarily with coughing, and in severe cases, air motion may be significantly impaired such that no wheezing is heard.

Signs which occur during an asthma attack include the use of accessory muscles of respiration (sternocleidomastoid and scalene muscles of the neck), there may be a paradoxical pulse (a pulse that is weaker during inhalation and stronger during exhalation), and over-inflation of the chest, a blue color of the skin and nails may occur from lack of oxygen.

In a mild exacerbation the peak expiratory flow rate (PEFR) is ≥200 L/min or ≥50% of the predicted best. Moderate is defined as between 80 and 200 L/min or 25% and 50% of the predicted best while severe is defined as ≤ 80 L/min or ≤25% of the predicted best.

Insufficient levels of vitamin D are linked with severe asthma attacks.

Status asthmaticus

Status asthmaticus is an acute exacerbation of asthma that does not respond to standard treatments of bronchodilators and steroids. Nonselective beta blockers (such as Timolol) have caused fatal status asthmaticus.

Exercise induced

A diagnosis of asthma is common among top athletes. One survey of participants in the 1996 Summer Olympic Games, in Atlanta, Georgia, U.S., showed that 15% had been diagnosed with asthma, and that 10% were on asthma medication.

There appears to be a relatively high incidence of asthma in sports such as cycling, mountain biking, and long-distance running, and a relatively lower incidence in

weightlifting and diving. It is unclear how much of these disparities are from the effects of training in the sport.

Exercise induced asthma can be treated with the use of a short-acting beta2 agonist.

Occupational

Asthma as a result of (or worsened by) workplace exposures is a commonly reported occupational respiratory disease. Still most cases of occupational asthma are not reported or are not recognized as such. Estimates by the American Thoracic Society (2004) suggest that 15–23% of new-onset asthma cases in adults are work related. In one study monitoring workplace asthma by occupation, the highest percentage of cases occurred among operators, fabricators, and laborers (32.9%), followed by managerial and professional specialists (20.2%), and in technical, sales, and administrative support jobs (19.2%). Most cases were associated with the manufacturing (41.4%) and services (34.2%) industries. Animal proteins, enzymes, flour, natural rubber latex, and certain reactive chemicals are commonly associated with work-related asthma. When recognized, these hazards can be mitigated, dropping the risk of disease.

Signs and symptoms

Common symptoms of asthma include wheezing, shortness of breath, chest tightness and coughing. Symptoms are often worse at night or in the early morning, or in response to exercise or cold air. Some people with asthma only rarely experience symptoms, usually in response to triggers, whereas other may have marked persistent airflow obstruction.

Gastro-esophageal reflux disease

Gastro-esophageal reflux disease coexists with asthma in 80% of people with asthma, with similar symptoms. This is due to increased lung pressures, promoting bronchoconstriction, and through chronic aspiration.

Sleep Disorders

Due to altered anatomy of the respiratory tract: increased upper airway adipose deposition, altered pharynx skeletal morphology, and extension of the pharyngeal airway; leading to upper airway collapse.

Cause

Asthma is caused by environmental and genetic factors. These factors influence how severe asthma is and how well it responds to medication. The interaction is complex and not fully understood.

Studying the prevalence of asthma and related diseases such as eczema and hay fever have yielded important clues about some key risk factors. The strongest risk factor for

developing asthma is a history of atopic disease; this increases one's risk of hay fever by up to 5x and the risk of asthma by 3-4x. In children between the ages of 3-14, a positive skin test for allergies and an increase in immunoglobulin E increases the chance of having asthma. In adults, the more allergens one reacts positively to in a skin test, the higher the odds of having asthma.

Because much allergic asthma is associated with sensitivity to indoor allergens and because Western styles of housing favor greater exposure to indoor allergens, much attention has focused on increased exposure to these allergens in infancy and early childhood as a primary cause of the rise in asthma. Primary prevention studies aimed at the aggressive reduction of airborne allergens in a home with infants have shown mixed findings. Strict reduction of dust mite allergens, for example, reduces the risk of allergic sensitization to dust mites, and modestly reduces the risk of developing asthma up until the age of 8 years old. However, studies also showed that the effects of exposure to cat and dog allergens worked in the converse fashion; exposure during the first year of life was found to *reduce* the risk of allergic sensitization and of developing asthma later in life.

The inconsistency of this data has inspired research into other facets of Western society and their impact upon the prevalence of asthma. One subject that appears to show a strong correlation is the development of asthma and obesity. In the United Kingdom and United States, the rise in asthma prevalence has echoed an almost epidemic rise in the prevalence of obesity. In Taiwan, symptoms of allergies and airway hyper-reactivity increased in correlation with each 20% increase in body-mass index. Several factors associated with obesity may play a role in the pathogenesis of asthma, including decreased respiratory function due to a buildup of adipose tissue (fat) and the fact that adipose tissue leads to a pro-inflammatory state, which has been associated with non-eosinophilic asthma.

Asthma has been associated with Churg–Strauss syndrome, and individuals with immunologically mediated urticaria may also experience systemic symptoms with generalized urticaria, rhino-conjunctivitis, orolaryngeal and gastrointestinal symptoms, asthma, and, at worst, anaphylaxis. Additionally, adult-onset asthma has been associated with periocular xanthogranulomas.

Environmental

Many environmental risk factors have been associated with asthma development and morbidity in children.

Maternal tobacco smoking during pregnancy and after delivery is associated with a greater risk of asthma-like symptoms, wheezing, and respiratory infections during childhood. Low air quality, from traffic pollution or high ozone levels, has been repeatedly associated with increased asthma morbidity and has a suggested association with asthma development that needs further research.

Recent studies show a relationship between exposure to air pollutants (e.g. from traffic) and childhood asthma. This research finds that both the occurrence of the disease and exacerbation of childhood asthma are affected by outdoor air pollutants. High levels of endotoxin exposure may contribute to asthma risk.

Viral respiratory infections are not only one of the leading triggers of an exacerbation but may increase one's risk of developing asthma especially in young children.

Psychological stress has long been suspected of being an asthma trigger, but only in recent decades has convincing scientific evidence substantiated this hypothesis. Rather than stress directly causing the asthma symptoms, it is thought that stress modulates the immune system to increase the magnitude of the airway inflammatory response to allergens and irritants.

Antibiotic use early in life has been linked to development of asthma in several examples; it is thought that antibiotics make children who are predisposed to atopic immune responses susceptible to development of asthma because they modify gut flora, and thus the immune system (as described by the hygiene hypothesis). The hygiene hypothesis (see below) is a hypothesis about the cause of asthma and other allergic disease, and is supported by epidemiologic data for asthma. All of these things may negatively affect exposure to beneficial bacteria and other immune system modulators that are important during development, and thus may cause an increased risk for asthma and allergy.

Caesarean sections have been associated with asthma, possibly because of modifications to the immune system (as described by the hygiene hypothesis).

Respiratory infections such as rhinovirus, *Chlamydia pneumoniae* and *Bordetella pertussis* are correlated with asthma exacerbations.

Beta blocker medications such as metoprolol may trigger asthma in those who are susceptible.

Observational studies have found that indoor exposure to volatile organic compounds (VOCs) may be one of the triggers of asthma, however experimental studies have not confirmed these observations. Even VOC exposure at low levels has been associated with an increase in the risk of pediatric asthma. Because there are so many VOCs in the air, measuring total VOC concentrations in the indoor environment may not represent the exposure of individual compounds. Exposure to VOCs is associated with an increase in the IL-4 producing Th2 cells and a reduction in IFN-γ producing Th1 cells. Thus the mechanism of action of VOC exposure may be allergic sensitization mediated by a Th2 cell phenotype. Different individual variations in discomfort, from no response to excessive response, were seen in one of the studies. These variations may be due to the development of tolerance during exposure. Another study has concluded that formaldehyde may cause asthma-like symptoms. Low VOC emitting materials should be used while doing repairs or renovations which decreases the symptoms related to asthma caused by VOCs and formaldehyde. In another study "the indoor concentration of

aliphatic compounds (C8-C11), butanols, and 2,2,4-trimethyl 1,3-pentanediol diisobutyrate (TXIB) was significantly elevated in newly painted dwellings. The total indoor VOC was about 100 micrograms/m3 higher in dwellings painted in the last year". The author concluded that some VOCs may cause inflammatory reactions in the airways and may be the reason for asthmatic symptoms.

There is a significant association between asthma-like symptoms (wheezing) among preschool children and the concentration of DEHP (pthalates) in indoor environment. DEHP (di-ethylhexyl phthalate) is a plasticizer that is commonly used in building material. The hydrolysis product of DEHP (di-ethylhexyl phthalate) is MEHP (Mono-ethylhexyl phthalate) which mimics the prostaglandins and thromboxanes in the airway leading to symptoms related to asthma. Another mechanism that has been studied regarding phthalates causation of asthma is that high phthalates level can "modulate the murine immune response to a coallergen". Asthma can develop in the adults who come in contact with heated PVC fumes. Two main type of phthalates, namely n-butyl benzyl phthalate (BBzP) and di(2-ethylhexyl) phthalate (DEHP), have been associated between the concentration of polyvinyl chloride (PVC) used as flooring and the dust concentrations. Water leakage were associated more with BBzP, and buildings construction were associated with high concentrations of DEHP. Asthma has been shown to have a relationship with plaster wall materials and wall-to wall carpeting. The onset of asthma was also related to the floor–leveling plaster at home. Therefore, it is important to understand the health aspect of these materials in the indoor surfaces.

Genetic

Over 100 genes have been associated with asthma in at least one genetic association study. However, such studies must be repeated to ensure the findings are not due to chance. Through the end of 2005, 25 genes had been associated with asthma in six or more separate populations:

- GSTM1
- IL10
- CTLA-4
- SPINK5
- LTC4S
- LTA
- GRPA
- NOD1
- CC16
- GSTP1
- STAT6
- NOS1
- CCL5
- TBXA2R
- TGFB1
- IL4
- IL13
- CD14
- ADRB2 (β-2 adrenergic receptor)
- HLA-DRB1
- HLA-DQB1
- TNF
- FCER1B
- IL4R
- ADAM33

Many of these genes are related to the immune system or to modulating inflammation. However, even among this list of highly replicated genes associated with asthma, the results have not been consistent among all of the populations that have been tested. This indicates that these genes are not associated with asthma under every condition, and that researchers need to do further investigation to figure out the complex interactions that cause asthma. One theory is that asthma is a collection of several diseases, and that genes might have a role in only subsets of asthma. For example, one group of genetic

differences (single nucleotide polymorphisms in 17q21) was associated with asthma that develops in childhood.

Gene–environment interactions

CD14-endotoxin interaction based on CD14 SNP C-159T

Endotoxin levels	CC genotype	TT genotype
High exposure	Low risk	High risk
Low exposure	High risk	Low risk

Research suggests that some genetic variants may only cause asthma when they are combined with specific environmental exposures, and otherwise may not be risk factors for asthma.

The genetic trait, CD14 single nucleotide polymorphism (SNP) C-159T and exposure to endotoxin (a bacterial product) are a well-replicated example of a gene-environment interaction that is associated with asthma. Endotoxin exposure varies from person to person and can come from several environmental sources, including environmental tobacco smoke, dogs, and farms. Researchers have found that risk for asthma changes based on a person's genotype at CD14 C-159T and level of endotoxin exposure.

Exacerbation

Some individuals will have stable asthma for weeks or months and then suddenly develop an episode of acute asthma. Different asthmatic individuals react differently to various factors. However, most individuals can develop severe exacerbation of asthma from several triggering agents.

Home factors that can lead to exacerbation include dust, house mites, animal dander (especially cat and dog hair), cockroach allergens and molds at any given home. Perfumes are a common cause of acute attacks in females and children. Both virus and bacterial infections of the upper respiratory tract infection can worsen asthma.

Hygiene hypothesis

One theory for the cause of the increase in asthma prevalence worldwide is the "hygiene hypothesis" —that the rise in the prevalence of allergies and asthma is a direct and unintended result of reduced exposure to a wide variety of different bacteria and virus types in modern societies, or modern hygienic practices preventing childhood infections. Children living in less hygienic environments (East Germany vs. West Germany, families with many children, day care environments) tend to have lower incidences of asthma and allergic diseases. This seems to run counter to the logic that viruses are often causative agents in exacerbation of asthma. Additionally, other studies have shown that viral infections of the lower airway may in some cases *induce* asthma, as a history of bronchiolitis or croup in early childhood is a predictor of asthma risk in later life. Studies

which show that upper respiratory tract infections are protective against asthma risk also tend to show that lower respiratory tract infections conversely tend to increase the risk of asthma.

Socioeconomic factors

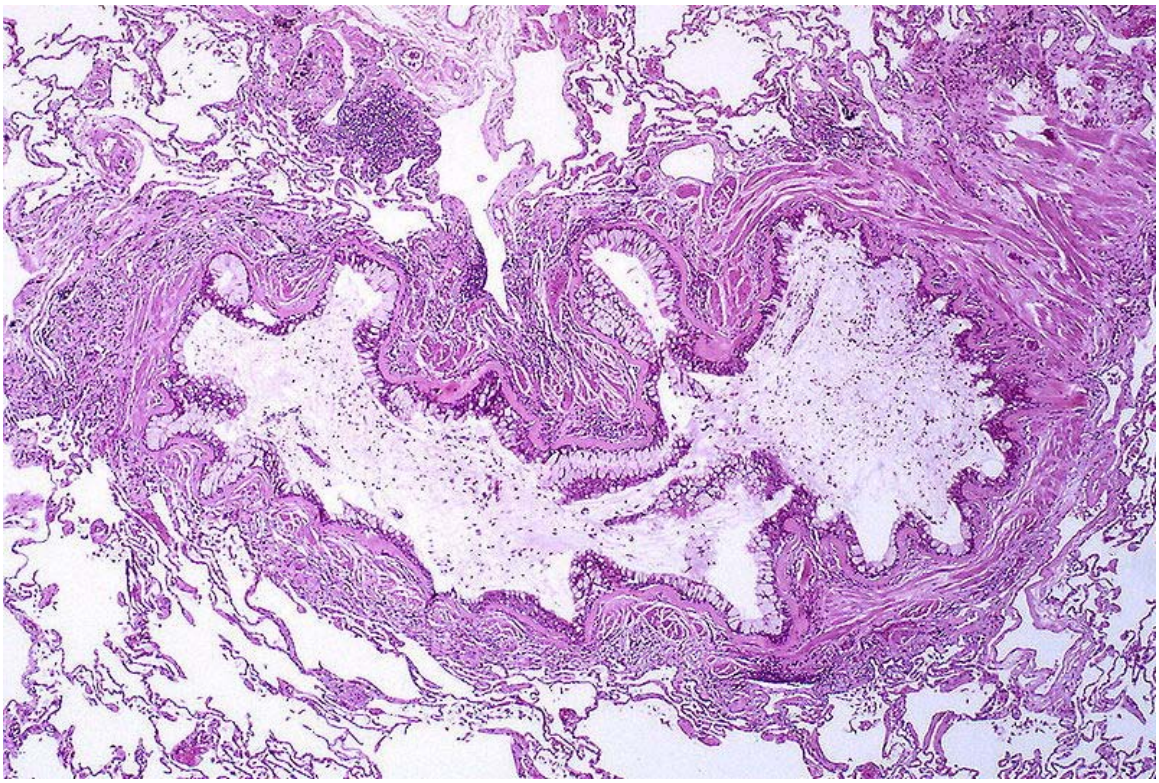
The incidence of asthma is highest among low-income populations worldwide. Asthma deaths are most common in low and middle income countries, and in the Western world, it is found in those low-income neighborhoods whose populations consist of large percentages of ethnic minorities. Additionally, asthma has been strongly associated with the presence of cockroaches in living quarters; these insects are more likely to be found in those same neighborhoods.

Most likely due to income and geography, the incidence of and treatment quality for asthma varies among different racial groups. The prevalence of "severe persistent" asthma is also greater in low-income communities than those with better access to treatment.

Diagnosis

<table>
<tr><th colspan="3">Severity of acute asthma exacerbations</th></tr>
<tr><td>Near-fatal asthma</td><td colspan="2">High $PaCO_2$ and/or requiring mechanical ventilation</td></tr>
<tr><td rowspan="8">Life threatening asthma</td><td colspan="2">Any one of the following in a person with severe asthma:-</td></tr>
<tr><td>Clinical signs</td><td>Measurements</td></tr>
<tr><td>Altered level of consciousness</td><td>Peak flow < 33%</td></tr>
<tr><td>Exhaustion</td><td>Oxygen saturation < 92%</td></tr>
<tr><td>Arrhythmia</td><td>PaO_2 < 8 kPa</td></tr>
<tr><td>Low blood pressure</td><td>"Normal" $PaCO_2$</td></tr>
<tr><td>Cyanosis</td><td rowspan="3"></td></tr>
<tr><td>Silent chest</td></tr>
<tr><td>Poor respiratory effort</td></tr>
<tr><td rowspan="2">Acute severe asthma</td><td colspan="2">Any one of:-</td></tr>
<tr><td colspan="2">Peak flow 33-50%</td></tr>
</table>

	Respiratory rate ≥ 25 breaths per minute
	Heart rate ≥ 110 beats per minute
	Unable to complete sentences in one breath
Moderate asthma exacerbation	Worsening symptoms
	Peak flow 80%-50% best or predicted
	No features of acute severe asthma



Obstruction of the lumen of the bronchiole by mucoid exudate, goblet cell metaplasia, epithelial basement membrane thickening and severe inflammation of bronchiole in a patient with asthma

There is currently not a precise physiologic, immunologic, or histologic test for diagnosing asthma. The diagnosis is usually made based on the pattern of symptoms (airways obstruction and hyperresponsiveness) and/or response to therapy (partial or complete reversibility) over time.

The British Thoracic Society determines a diagnosis of asthma using a ‘response to therapy’ approach. If the patient responds to treatment, then this is considered to be a confirmation of the diagnosis of asthma. The response measured is the reversibility of airway obstruction after treatment. Airflow in the airways is measured with a peak flow

meter or spirometer, and the following diagnostic criteria are used by the British Thoracic Society:

- ≥20% difference on at least three days in a week for at least two weeks;
- ≥20% improvement of peak flow following treatment, for example:
  - 10 minutes of inhaled β-agonist (e.g., salbutamol);
  - six weeks of inhaled corticosteroid (e.g., beclometasone);
  - 14 days of 30 mg prednisolone.
- ≥20% decrease in peak flow following exposure to a trigger (e.g., exercise).

In contrast, the US National Asthma Education and Prevention Program (NAEPP) uses a 'symptom patterns' approach. Their guidelines for the diagnosis and management of asthma state that a diagnosis of asthma begins by assessing if any of the following list of indicators is present. While the indicators are not sufficient to support a diagnosis of asthma, the presence of multiple key indicators increases the probability of a diagnosis of asthma. Spirometry is needed to establish a diagnosis of asthma.

- Wheezing—high-pitched whistling sounds when breathing out—especially in children. (Lack of wheezing and a normal chest examination do not exclude asthma.)
- history of any of the following:
  - Cough, worse particularly at night
  - Recurrent wheeze
  - Recurrent difficulty in breathing
  - Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
  - Exercise
  - Viral infection
  - Animals with fur or hair
  - House-dust mites (in mattresses, pillows, upholstered furniture, carpets)
  - Mold
  - Smoke (tobacco, wood)
  - Pollen
  - Changes in weather
  - Strong emotional expression (laughing or crying hard)
  - Airborne chemicals or dusts
  - Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient

The latest guidelines from the U.S. National Asthma Education and Prevention Program (NAEPP) recommend spirometry at the time of initial diagnosis, after treatment is initiated and symptoms are stabilized, whenever control of symptoms deteriorates, and every 1 or 2 years on a regular basis. The NAEPP guidelines do not recommend testing peak expiratory flow as a regular screening method because it is more variable than spirometry. However, testing peak flow at rest (or baseline) and after exercise can be helpful, especially in young patients who may experience only exercise-induced asthma.

It may also be useful for daily self-monitoring and for checking the effects of new medications. Peak flow readings can be charted together with a record of symptoms or use peak flow charting software. This allows patients to track their peak flow readings and pass information back to their doctor or nurse.

Differential diagnosis

Differential diagnoses include:

- Infants and Children
  - Upper airway diseases
    - Allergic rhinitis and sinusitis
  - Obstructions involving large airways
    - Foreign body in trachea or bronchus
    - Vocal cord dysfunction
    - Vascular rings or laryngeal webs
    - Laryngotracheomalacia, tracheal stenosis, or bronchostenosis
    - Enlarged lymph nodes or tumor
  - Obstructions involving small airways
    - Viral bronchiolitis or obliterative bronchiolitis
    - Cystic fibrosis
    - Bronchopulmonary dysplasia
    - Heart disease
  - Other causes
    - Recurrent cough not due to asthma
    - Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux
    - Medication induced
- Adults
  - COPD (e.g., chronic bronchitis or emphysema)
  - Congestive heart failure
  - Pulmonary embolism
  - Mechanical obstruction of the airways (benign and malignant tumors)
  - Pulmonary infiltration with eosinophilia
  - Cough secondary to drugs (e.g., angiotensin-converting enzyme (ACE) inhibitors)
  - Vocal cord dysfunction

Before diagnosing asthma, alternative possibilities should be considered such as the use of known bronchoconstrictors (substances that cause narrowing of the airways, e.g. certain anti-inflammatory agents or beta-blockers). Among elderly people, the presenting symptom may be fatigue, cough, or difficulty breathing, all of which may be erroneously attributed to Chronic obstructive pulmonary disease(COPD), congestive heart failure, or simple aging.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease can coexist with asthma and can occur as a complication of chronic asthma. After the age of 65 most people with obstructive airway disease will have asthma and COPD. In this setting, COPD can be differentiated by increased airway neutrophils, abnormally increased wall thickness, and increased smooth muscle in the bronchi. However, this level of investigation is not performed due to COPD and asthma sharing similar principles of management: corticosteroids, long acting beta agonists, and smoking cessation. It closely resembles asthma in symptoms, is correlated with more exposure to cigarette smoke, an older age, less symptom reversibility after bronchodilator administration (as measured by spirometry), and decreased likelihood of family history of atopy.

Others

The term "atopy" was coined to describe this triad of atopic eczema, allergic rhinitis and asthma.

Pulmonary aspiration, whether direct due to dysphagia (swallowing disorder) or indirect (due to acid reflux), can show similar symptoms to asthma. However, with aspiration, fevers might also indicate aspiration pneumonia. Direct aspiration (dysphagia) can be diagnosed by performing a modified barium swallow test. If the aspiration is indirect (from acid reflux), then treatment is directed at this is indicated.

Prevention

The evidence for the effectiveness of measures to prevent the development of asthma is weak. Ones which show some promise include: limiting smoke exposure both in utero and after delivery, breastfeeding, increased exposure to respiratory infection per the hygiene hypothesis (such as in those who attend daycare or are from large families).

Management

A specific, customized plan for proactively monitoring and managing symptoms should be created. Someone who has asthma should understand the importance of reducing exposure to allergens, testing to assess the severity of symptoms, and the usage of medications. The treatment plan should be written down and adjusted according to changes in symptoms.

The most effective treatment for asthma is identifying triggers, such as cigarette smoke, pets, or aspirin, and eliminating exposure to them. If trigger avoidance is insufficient, medical treatment is recommended. Medical treatments used depends on the severity of illness and the frequency of symptoms. Specific medications for asthma are broadly classified in to fast acting and long acting.

Bronchodilators are recommended for short-term relief of symptoms. In those with occasional attacks, no other medication is needed. If mild persistent disease is present (more than two attacks a week), low-dose inhaled glucocorticoids or alternatively, an oral leukotriene antagonist or a mast cell stabilizer is recommended. For those who suffer daily attacks, a higher dose of inhaled glucocorticoid is used. In a severe asthma exacerbation, oral glucocorticoids are added to these treatments.

Lifestyle modification

Avoidance of triggers is a key component of improving control and preventing attacks. The most common triggers include: allergens, smoke (tobacco and other), air pollution, non selective beta-blockers, and sulfite-containing foods.

Medications

Medications used to treat asthma are divided into two general classes: quick-relief medications used to treat acute symptoms; and long-term control medications used to prevent further exacerbation.

Fast acting

Salbutamol metered dose inhaler commonly used to treat asthma attacks

- Short acting beta$_2$-adrenoceptor agonists (SABA), such as salbutamol (*albuterol* USAN) are the first line treatment for asthma symptoms.
- Anticholinergic medications, such as ipratropium bromide provide addition benefit when used in combination with SABA in those with moderate or severe symptoms. Anticholinergic bronchodilators can also be used if a person cannot tolerate a SABA.
- Older, less selective adrenergic agonists, such as inhaled epinephrine, have similar efficacy to SABAs. They are however not recommended due to concerns regarding excessive cardiac stimulation.

Long term control

Fluticasone propionate metered dose inhaler commonly used for long term control

- Glucocorticoids are the most effective treatment available for long term control. Inhaled forms are usually used except in the case of severe persistent disease, in which oral steroids may be needed. Inhaled formulations may be used once or twice daily, depending on the severity of symptoms.

- Long acting beta-adrenoceptor agonists (LABA) have at least a 12-hour effect. They are however not to be used without a steroid due to an increased risk of severe symptoms. In December 2008, members of the FDA's drug-safety office recommended withdrawing approval for these medications in children. Discussion is ongoing about their use in adults.

- Leukotriene antagonists (such as zafirlukast) are an alternative to inhaled glucocorticoids, but are not preferred. They may also be used in addition to inhaled glucocorticoids but in this role are second line to LABA.
- Mast cell stabilizers (such as cromolyn sodium) are another non-preferred alternative to glucocorticoids.

Delivery methods

Medications are typically provided as metered-dose inhalers (MDIs) in combination with an asthma spacer or as a dry powder inhaler. The spacer is a plastic cylinder that mixes the medication with air, making it easier to receive a full dose of the drug. A nebulizer may also be used. Nebulizers and spacers are equally effective in those with mild to moderate symptoms however insufficient evidence is available to determine whether or not a difference exist in those severe symptomatology.

Safety and adverse effects

Long-term use of glucocorticoids carries a significant potential for adverse effects. The incidence of cataracts is increased in people undergoing treatment for asthma with corticosteroids, due to altered regulation of lens epithelial cells. The incidence of osteoporosis is also increased, due to changes inbone remodeling.

Other

When an asthma attack is unresponsive to usual medications, other options are available for emergency management.

- Oxygen is used to alleviate hypoxia if saturations fall below 92%.
- Magnesium sulfate intravenous treatment has been shown to provide a bronchodilating effect when used in addition to other treatment in severe acute asthma attacks.
- Heliox, a mixture of helium and oxygen, may also be considered in severe unresponsive cases.
- Intravenous salbutamol is not supported by available evidence and is thus used only in extreme cases.
- Methylxanthines (such as theophylline) were once widely used, but do not add significantly to the effects of inhaled beta-agonists.
- The dissociative anesthetic ketamine is theoretically useful if intubation and mechanical ventilation is needed in people who are approaching respiratory arrest; however, there is no evidence from clinical trials to support this.

Complementary medicine

Many asthma patients, like those who suffer from other chronic disorders, use alternative treatments; surveys show that roughly 50% of asthma patients use some form of unconventional therapy. There is little data to support the effectiveness of most of these

therapies. Evidence is insufficient to support the usage of Vitamin C. Acupuncture is not recommended for the treatment as there is insufficient evidence to support its use. Air ionisers show no evidence that they improve asthma symptoms or benefit lung function; this applied equally to positive and negative ion generators.

Dust mite control measures, including air filtration, chemicals to kill mites, vacuuming, mattress covers and others methods had no effect on asthma symptoms. However, a review of 30 studies found that "bedding encasement might be an effective asthma treatment under some conditions" (when the patient is highly allergic to dust mite and the intervention reduces the dust mite exposure level from high levels to low levels). Washing laundry/rugs in hot water was also found to improve control of allergens.

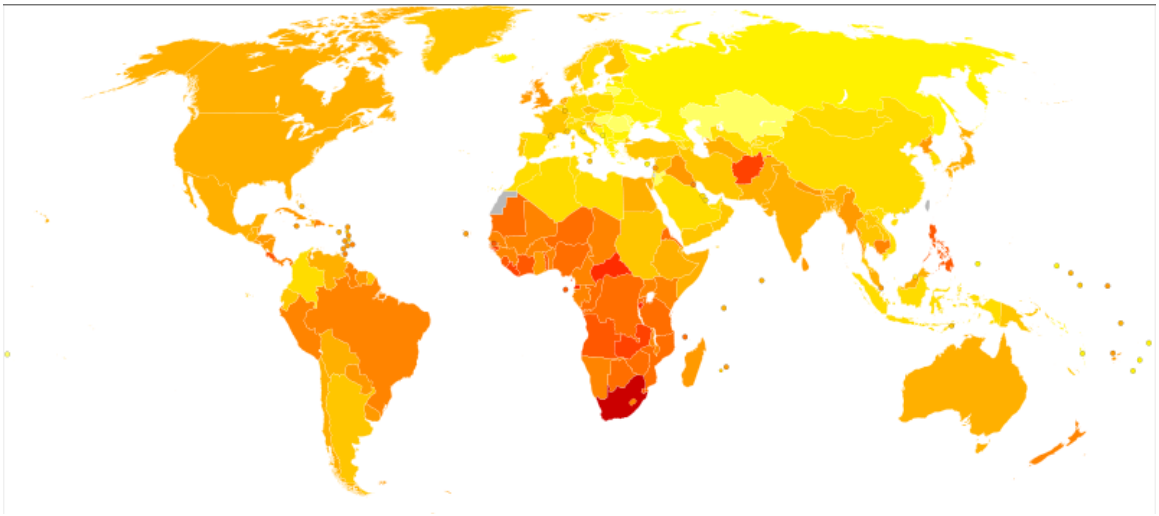
A study of "manual therapies" for asthma, including osteopathic, chiropractic, physiotherapeutic and respiratory therapeutic manoeuvres, found there is insufficient evidence to support or refute their use in treating. The Buteyko breathing technique for controlling hyperventilation may result in a reduction in medications use however does not have any effect on lung function. Thus an expert panel felt that evidence was insufficient to support its use.

Prognosis

The prognosis for asthma is good, especially for children with mild disease. Of asthma diagnosed during childhood, 54% of cases will no longer carry the diagnosis after a decade. The extent of permanent lung damage in people with asthma is unclear. Airway remodeling is observed, but it is unknown whether these represent harmful or beneficial changes. Although conclusions from studies are mixed, most studies show that early treatment with glucocorticoids prevents or ameliorates decline in lung function as measured by several parameters. For those who continue to suffer from mild symptoms, corticosteroids can help most to live their lives with few disabilities. It is more likely to consider immediate medication of inhaled corticosteroids as soon as asthma attacks occur. According to studies conducted, patients with relatively mild asthma who have received inhaled corticosteroids within 12 months of their first asthma symptoms achieved good functional control of asthma after 10 years of individualized therapy as compared to patients who received this medication after 2 years (or more) from their first attacks. Though they (delayed) also had good functional control of asthma, they were observed to exhibited slightly less optimal disease control and more signs of airway inflammation.

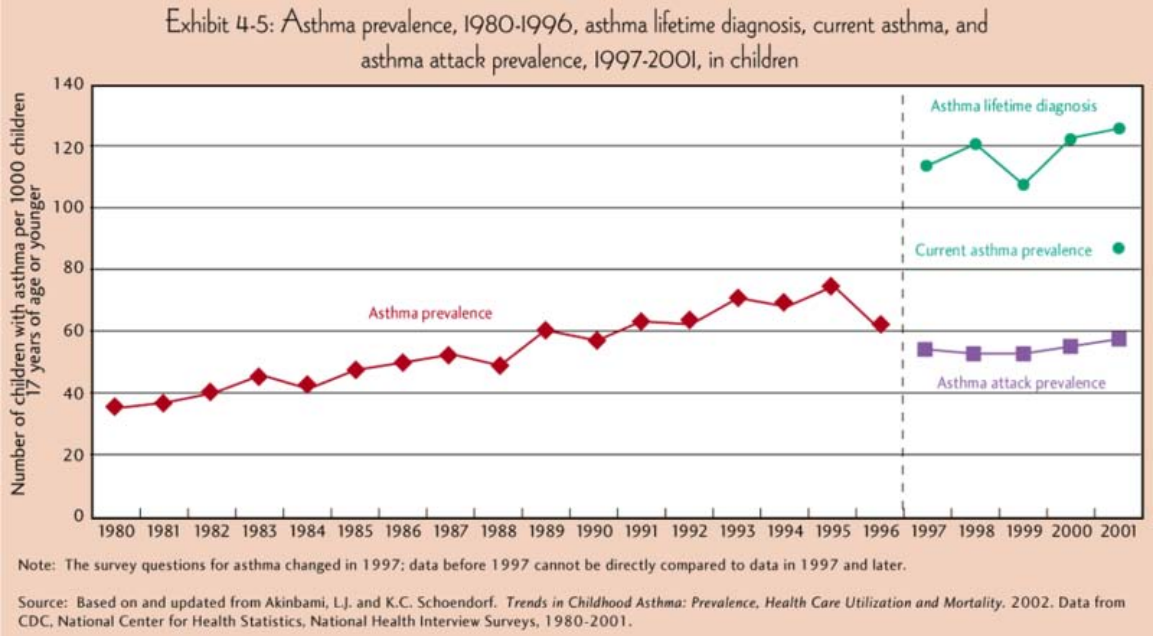
Asthma mortality has decreased over the last few decades due to better recognition and improvement in care.

Epidemiology



Disability-adjusted life year for asthma per 100,000 inhabitants in 2004

- no data
- <100
- 100–150
- 150–200
- 200–250
- 250–300
- 300–350
- 350–400
- 400–450
- 450–500
- 500–550
- 550–600
- >600



The prevalence of childhood asthma in the United States has increased since 1980, especially in younger children.

As of 2009, 300 million people worldwide were affected by asthma leading to approximately 250,000 deaths per year.

It is estimated that asthma has a 7-10% prevalence worldwide. As of 1998, there was a great disparity in prevalence worldwide across the world (as high as a 20 to 60-fold difference), with a trend toward more developed and westernized countries having higher rates of asthma. Westernization however does not explain the entire difference in asthma prevalence between countries, and the disparities may also be affected by differences in genetic, social and environmental risk factors. Mortality however is most common in low to middle income countries, while symptoms were most prevalent (as much as 20%) in the United Kingdom, Australia, New Zealand, and Republic of Ireland; they were lowest (as low as 2–3%) in Eastern Europe, Indonesia, Greece, Uzbekistan, India, and Ethiopia.

While asthma is more common in affluent countries, it is by no means a restricted problem; the WHO estimate that there are between 15 and 20 million people with asthma in India. In the U.S., urban residents, Hispanics, and African Americans are affected more than the population as a whole. Striking increases in asthma prevalence have been observed in populations migrating from a rural environment to an urban one, or from a third-world country to Westernized one.

Asthma affects approximately 7% of the population of the United States and 5% of people in the United Kingdom. Asthma causes 4,210 deaths per year in the United States. In 2005 in the United States asthma affected more than 22 million people including 6 million children. It accounted for nearly 1/2 million hospitalizations. More boys have asthma than girls, but more women have it than men. Of all children, African Americans

and Latinos who live in cities are more at risk for developing asthma. African American children in the U.S. are four times more likely to die of asthma and three times more likely to be hospitalized, compared to their white counterparts. In some Latino neighborhoods, as many as one in three children has been found to have asthma.

In England, an estimated 261,400 people were newly diagnosed with asthma in 2005; 5.7 million people had an asthma diagnosis and were prescribed 32.6 million asthma-related prescriptions.

The frequency of atopic dermatitis, asthma, urticaria and allergic contact dermatitis has been found to be lower in psoriatic patients.

Increasing frequency

Rates of asthma have increased significantly between the 1960s and 2008. Some 9% of US children had asthma in 2001, compared with just 3.6% in 1980. The World Health Organization (WHO) reports that some 10% of the Swiss population suffers from asthma today, compared with just 2% some 25–30 years ago.

Variability

Asthma prevalence in the US is higher than in most other countries in the world, but varies drastically between diverse US populations. In the US, asthma prevalence is highest in Puerto Ricans, African Americans, Filipinos, Irish Americans, and Native Hawaiians, and lowest in Mexicans and Koreans. Mortality rates follow similar trends, and response to salbutamol is lower in Puerto Ricans than in African Americans or Mexicans. As with worldwide asthma disparities, differences in asthma prevalence, mortality, and drug response in the US may be explained by differences in genetic, social and environmental risk factors.

Asthma prevalence also differs between populations of the same ethnicity who are born and live in different places. US-born Mexican populations, for example, have higher asthma rates than non-US born Mexican populations that are living in the US.

There is no correlation between asthma and gender in children. More adult women are diagnosed with asthma than adult men, but this does not necessarily mean that more adult women have asthma.

History

Asthma was first recognized and named by Hippocrates circa 450 BC. During the 1930s–50s, asthma was considered as being one of the 'holy seven' psychosomatic illnesses. Its aetiology was considered to be psychological, with treatment often based on psychoanalysis and other 'talking cures'. As these psychoanalysts interpreted the asthmatic wheeze as the suppressed cry of the child for its mother, so they considered that the treatment of depression was especially important for individuals with asthma.

Research

- The University of Maryland School of Medicine announced in 2010 that bitter taste receptors had been discovered on smooth muscle in human lung bronchi. These smooth muscles control airway contraction and dilation - contrary to expectation, bitter substances such as quinine or chloroquine opened contracted airways, offering new insight into asthma.

Chapter 9

Brittle Asthma and Status Asthmaticus

Brittle asthma

Brittle asthma is a term used to describe two rare phenotypes of asthma distinguishable by recurrent, severe attacks.

The subtypes are divided by symptoms into either Type 1 or Type 2, depending on the stability of the patient's maximum speed of expiration, or peak expiratory flow rate (PEFR). Type 1 is characterized by sustained, chronic variability of PEFR, while type 2 is distinguished by sudden unpredictable drops in PEFR where asthma symptoms are otherwise well controlled and the function of the lungs is not substantially impaired.

Brittle asthma is one of the "unstable" subtypes of "difficult asthma", a term used to characterize the less than 5% of asthma cases that do not respond to maximal inhaled treatment, including high doses of corticosteroids combined with additional therapies such as long-acting beta-2 agonists.

Characteristics

The 2005 *Oxford Textbook of Medicine* distinguishes type 1 brittle asthma by "persistent daily chaotic variability in peak flow (usually greater than 40 per cent diurnal variation in PEFR more than 50 per cent of the time)", while type 2 is identified by "sporadic sudden falls in PEFR against a background of usually well-controlled asthma with normal or near normal lung function". In both types, patients are subject to recurrent, severe attacks. The cardinal symptoms of an asthma attack are shortness of breath (dyspnea), wheezing, and chest tightness. Individuals with type 1 suffer chronic attacks in spite of ongoing medical therapy, while those with type 2 experience sudden, acute and even potentially life-threatening attacks even though otherwise their asthma seems well managed.

When first defined by Margaret Turner-Warwick in 1977, the term brittle asthma was used specifically to describe type 1, but as studies into the phenotype were conducted the second type was also distinguished. The condition is rare. 1999's *Difficult Asthma* estimates a prevalence of approximately .05% brittle asthma sufferers among the asthmatic population. Though found in all ages, it is most commonly found in individuals between the ages of 18 and 55; it is present in both sexes, though type 1 has been

diagnosed in three times as many women as men. Hospitalization is more frequent for type 1 than type 2.

Treatment

In addition to any issues of treatment compliance, and maximised corticosteroids (inhalled or oral) and beta agonist, brittle asthma treat also involves for type 1 additional subcutaneous injections of beta2 agonist and inhalation of long acting beta-adrenoceptor agonist, whilst type 2 needs allergen avoidance and self-management approaches. Since catastrophic attacks are unpredictable in type 2, patients may display identification of the issue, such as a MedicAlert bracelet, and carry an epinephrine autoinjector.

Status asthmaticus

Status asthmaticus	
ICD-10	J46.
ICD-9	493.01, 493.91
eMedicine	article/302238
MeSH	D013224

Status asthmaticus is an acute exacerbation of asthma that does not respond to standard treatments of bronchodilators and steroids. Symptoms include chest tightness, rapidly progressive dyspnea (shortness of breath), dry cough, use of accessory muscles, labored breathing and extreme wheezing. It is a life-threatening episode of airway obstruction considered a medical emergency. Complications include cardiac and/or respiratory arrest.

The lung failure means that oxygen can no longer be provided, carbon dioxide can no longer be eliminated, which leads to acidosis.

It is characterized histologically by smooth muscle hypertrophy and basement membrane thickening.

Interventions include initiating and maintaining IV access, bronchodilators as prescribed, telemetry monitoring in the PCU, usually arterial blood gas tests, sometimes arterial lines are inserted and preparing for emergency intubation.

Intravenous treatments such as Corticosteroids, Aminophylline, Theophylline and Salbutamol are typically given. Many patients eventually respond avoiding more aggressive measures.

Status Asthmaticus does not respond adequately to nebulised treatment alone therefore the intravenous treatments such as those above sometimes in addition to Intravenous Magnesium Sulphate are also given.

Chapter 10

Occupational Asthma

Occupational asthma is an occupational condition defined as:

"a disease characterized by variable airflow limitation and/or airway hyper-responsiveness due to causes and conditions attributable to a particular occupational environment and not stimuli encountered outside the workplace".

Asthma is defined as a respiratory disease caused by narrowing of the air passages. It is synonymous with difficulty in breathing, tightness of chest, nasal irritation, coughing and wheezing. The first person to use it in reference to a medical condition was Hippocrates, and he believed that tailors, anglers and metalworkers were more likely to be affected by the disease. Although much research has been done since, the inflammatory component of asthma was recognized only in the 1960s.

Today, asthma affects as much as 15% of the Canadian population (and this is true of other developed countries too) and has increased fourfold in the last 20 years. Various reasons can be identified for this increase - Of course better diagnosis and facilities along with a greater awareness regarding the disease have played a major role. But, one cannot deny the part of increased environmental pollution. Researchers have been working on the relation between the environment and human health since long and the air we breathe is the primary cause for lung diseases like asthma, rhinitis, COPDs, etc. that affect us today.

Approximately 10 to 15% of the adults affected by the disease report an aggravation of their symptoms while at work and an improvement when away, which implies that they may be suffering from Occupational Asthma. Thus, when an individual’s Asthma is caused, not aggravated, by workplace materials, it is defined as Occupational Asthma. In the USA, OA is considered the most common occupational lung disease. At present, over 400 workplace substances have been identified as having asthmagenic or allergenic properties. Their existence and magnitude vary from region to region and the type of industry and can be as varied as wood dust (cedar, ebony, etc.), persulfates (Hairsprays), zinc or even seafood like prawns. For example, in France the industries most affected in order of importance are Bakeries and cake-shops, automobile industry and hairdressers, whereas in Canada the principal cause is wood dust, followed by isocyanates.

Hypersensitivity pneumonitis is a related condition, with many occupational examples (e.g. "Farmer's Lung", "Malt Worker's Lung" and "Humidifier Lung" etc.). However, although overlapping in many cases, hypersensitivity pneumonitis may be distinguished from *occupational asthma* in that it isn't restricted to only occupational exposure, and involves type III hypersensitivity and type IV hypersensitivity rather than type I hypersensitivity of asthma. Unlike asthma, hypersensitivity pneumonitis targets lung alveoli rather than bronchi.

Signs and symptoms

Less than five years of exposure to an occupational agent can be enough for the appearance of the first OA symptoms. This depends on whether the reason for the OA to occur was exposure to the causative agent over a period of time (with a latency period) or a single exposure to an irritant but at a very high concentration (without latency period). Both eventually result in OA. Coughing, wheezing, nasal irritation, difficulty in breathing, tightness of chest are the most common symptoms and can be recognized more easily by asking oneself the following questions:

1. Are any of the above symptoms recurrent/chronic?
2. Are they present at work?
3. Do they worsen towards the end of the work day and/or end of the week?
4. Does the employee/worker feel an improvement in his condition when away from work, on vacation or on weekends?

If these symptoms persist, the person is most likely suffering from OA. However, one must be aware that this could also be because the person is already suffering from asthma and his condition was simply aggravated by workplace irritants (Work-aggravated asthma). In this case, although he will suffer similar consequences as someone who is suffering from OA (loss of work, medical expenses, etc.), his disease cannot be considered as having an occupational origin.

Diagnosis

Like for any other disease correct diagnosis is important. According to Dr. Susan Tarlo:

“It is important to recognize, since if due to a workplace sensitizer and, if undetected and if the patient continues to work with even small exposure to the relevant sensitizing agent, the prognosis is worse”. She also concluded that, “the chance of eventual improvement in Asthma severity after stopping exposure decreases with the duration of exposure after the onset of the symptoms. The best chance of asthma clearing or significantly improving is associated with early diagnosis and early removal from ongoing exposure”.

However, the biggest challenge is the first step – Family doctors and patients alike do not have sufficient knowledge about Occupational Asthma - only 15% of the asthmatic patients are asked by their doctor if their symptoms are related to work. And often,

patients do not mention this possibility due to the fear of losing their jobs or simply because they are not aware of the association between their work and asthma. What they do not realize is that if they continue working under such circumstances, not only are they sure to lose their job in the long run but their asthma will also reach an irreversible stage. Clearly, an incorrect diagnosis will have considerable medical, social and financial consequences.

Diagnosis of OA is a process and has to be done over a period of time. First, the patient's occupational and clinical history is taken and his symptoms are charted (Charting is usually done at the end of a typical work week and within 24 hours of the occurrence of symptoms in order to get objective information). Once this has been established, the following **diagnostic methods** are used:

Non-specific bronchial hyperreactivity

A non-specific bronchial hyperreactivity test involves testing with methacoline, after which the Forced Expiratory Volume in 1 second (FEV_1) of the patient is measured. This test is often used for measuring the intensity of a person's asthma and to confirm that the person needs to be treated for asthma. Other non specific tests could even require the patient to run in open air or on a treadmill for a few minutes at a continuous pace. In this case, the individual's Peak Expiratory Flow Rate (PEFR) is measured. (The peak expiratory flow rate measures how fast a person can exhale).

Skin prick tests

Although called skin prick test, it does not involve drawing blood, in fact, the skin is not even scratched. It is usually performed on the inner aspect of the forearm where grid is marked (using a simple marker) and a drop of the allergen that is to be tested is placed on the arm at the end of each line. All the allergens that need to be tested can be similarly placed on the grid. Once this has been done, the skin is pricked through the drop using a lancet. Reactions, if any, occur within 10 to 15 minutes and these results can then be analyzed.

IgE-specific tests

Immunoglobulin E is an antibody found in our blood and is effective against toxins. Since it can also trigger allergic reactions to specific allergens like pollen, the IgE test is performed to evaluate whether the subject is allergic to these substances.

Spirometric tests

Conventionally, a spirometer can be defined as a device used to measure timed expired and inspired volumes. These volumes then enable us to measure how quickly the lungs can be emptied and filled and whether it is effective. These measurements need to be stated at body temperature, and the pressure will have to be saturated with water vapor to

get the correct values. This is because, if the spirometer is dry the recorded volume of air displaced is lower than that actually displaced by the lungs.

Peak Expiratory Flow at work

This test uses the PEFR method. The only difference is that it measures the functioning of the patient's airways at his place of work and not necessarily in a controlled environment. The patient breathes into a Peak Expiratory Flow monitor (a hand-held device that has a mouth piece at one end and a scale with an indicator on the other).

Specific inhalation challenge

- **Realistic method**
- "The Realistic Method" is a whole body sealed chamber where the patient is exposed to articles that are present in their workplace. This method has the advantage of being able to assess, albeit highly subjectively, ocular and nasal symptoms as well as a reduction in FEV_1.
- **Closed-circuit method**
- This test requires the patient to breathe aerosols of the suspected 'asthmagens' through an oro-facial mask. These 'asthmagens' are aerosolized using closed circuit chambers, and the quantities and concentrations administered being minute and extremely stable minimize the risk of exaggerated responses.

Of the above methods of doing a diagnosis, procedures such as monitoring of spirometry or peak expiratory flow at work and Specific Inhalation Challenges (SIC) have been proved as the most objective and reliable methods.

Prevention and treatment

According to the Canadian Centre for Occupational Health and Safety (CCOHS) better education of workers, management, unions and medical professionals is the key to the prevention of OA. This will enable them to identify the risk factors and put in place preventive measures like masks or exposure limits, etc.

Recovery is directly dependent on the duration and level of exposure to the causative agent. Depending on the severity of the case, the condition of the patient can improve dramatically during the first year after removal from exposure.

Three basic types of procedures are used for treating the affected workers:

1) Reducing exposure

This method is most effective for those affected by irritant-induced OA. Thus, by reducing their exposure duration and level to the causative agent, the probability of suffering another reaction is lowered. But exposure can be reduced in other ways like making use of face masks or providing better ventilation. Now, more and more di-

isocyanate free spray paints are available. Similarly, most hospitals and healthcare companies have exchanged latex gloves for other materials. Thus, reducing exposure to known asthmagens can also be used as a preventive measure.

2) Removal from exposure

Persons affected by OA that occurred after a latency period, whether a few months or years, must be immediately removed from exposure to the causative agent. This is their only chance of recovery. However, this entails severe socio-economic consequences for the worker as well as the employer due to loss of job, unemployment, compensation issues, quasi-permanent medical expenditures, hiring and re-training of new personnel, etc. Also, according to recent research the probability that those who suffer from OA remain unemployed longer than those who suffer from non-occupational asthma is higher. One solution to this problem is relocating the employee in the same company away from the causative agents.

3) Medical and pharmacological treatment

Anyone diagnosed with Asthma will have to undergo medical treatment. This is complementary to either removing or reducing the patient's exposure to the causal agents. Two types of medication can be used:

- **Relievers or bronchodilators**

  Short-acting beta-agonists like salbutamol or terbutaline or long-acting beta-agonists like salmeterol and formoterol or anticholinergic, etc. dilate airways which relieve the symptoms thus reducing the severity of the reaction. Some patients also use it just before work to avoid a drop in the FEV_1.

- **Preventers**
- Anti-inflammatory agents like corticosteroids, LKTRA or mast cell stabilizers can be used depending on the severity of the case.

History

In 1700, Bernardino Ramazzini, Doctor of Philosophy and Medicine from Parma, Italy published the book "De Morbis Artificum Diatriba" (A Treatise on the Diseases of Workers). Although researchers like Olaus Magus had done work on diseases due to occupational causes as early as 1555, this was the first comprehensive work on work-related diseases. This volume described in detail the diseases of workers in 52 different occupations. Thus, it was the basis for the emergence of occupational medicine and even today, it is an important reference. Due to his important contribution to this field, Dr. Ramazzini is considered the father of occupational medicine.

Similarly, for his contribution to research on asthma in the workplace, Dr Jack Pepys is considered as the Father of Occupational Asthma. His work on the role of Aspergillus

species in pulmonary diseases as also on the cause of farmer's lung have heavily influenced the emergence of OA as an occupational disease. And, thanks to his work on Specific Inhalation Challenge, the compensatible aspect of the disease was recognized.

Society and culture

Compensation

As mentioned earlier, when a person is diagnosed as having occupational asthma, it results in serious socio-economic consequences not only for the workers but also for the employer and the healthcare system. The employee has to be taken off job immediately to prevent any further damage to his health. And, the probability of being re-employed is lower for those suffering from OA as compared to those suffering from normal asthma. The employer not only pays compensation to the employee, but will also have to spend a considerable amount of time and energy and funds for hiring and training new personnel. In the United States, it was estimated that the direct cost of occupational asthma in 1996 was $1.2 billion and the indirect cost $0.4 billion, for a total cost of $1.6 billion.

Occupations at risk

The following tables show occupations that are known to be at risk for occupational asthma, and main substances involved.

Yet, the riskiest occupations for asthma are: adhesive handlers (e.g. acrylate), animal handlers and veterinarians (animal proteins), bakers and millers (cereal grains), carpet makers (gums), electronics workers (soldering resin), forest workers, carpenters and cabinetmakers (wood dust), hairdressers (e.g. persulfate), health care workers (latex and chemicals such as glutaraldehyde), janitors and cleaning staff (e.g. chloramine-T), pharmaceutical workers (drugs, enzymes), seafood processors, shellac handlers (e.g. amines), solderers and refiners (metals), spray painters, insulation installers, plastics and foam industry workers (e.g. diisocyanates), textile workers (dyes) and users of plastics and epoxy resins (e.g. anhydrides)

Grains, flours, plants and gums

Occupation	Agent
Bakers, millers	Wheat
Chemists, coffee bean baggers and handlers, gardeners, millers, oil industry workers, farmers	Castor beans
Cigarette factory workers	Tobacco dust
Drug manufacturers, mold makers in sweet factories, printers	Gum acacia

Isocyanates and metals

Occupation	Agent
Boat builders, foam manufacturers, office workers, plastics factory workers, refrigerator manufacturers, TDI manufacturers/users, printers, laminators, tinners, toy makers	TDI
Boiler cleaners, gas turbine cleaners	Vanadium

Farmers, grain handlers	Grain dust
Gum manufacturers, sweet makers	Gum tragacanth
Strawberry growers	Strawberry pollen
Tea sifters and packers	Tea dust
Tobacco farmers	Tobacco leaf
Woollen industry workers	Wool

Animals, insects and fungi

Occupation	Agent
Bird fanciers	Avian proteins
Cosmetic manufacturers	Carmine
Entomologists	Moths, butterflies
Feather pluckers	Feathers
Field contact workers	Crickets
Fish bait breeders	Bee moths
Flour mill workers, bakers, farm workers, grain handlers	Grain storage mites, alternaria, aspergillus
Laboratory workers	Locusts, cockroaches, grain weevils, rats, mice, guinea pigs, rabbits
Mushroom cultivators	Mushroom spores
Oyster farmers	Sea pineapples (Hoya)
Pea sorters	Mexican bean weevils
Pigeon breeders	Pigeons
Poultry workers	Chickens
Prawn processors	Prawns
Silkworm sericulturers	Silkworms
Zoological museum curators	Beetles

Chemicals/Materials

Car sprayers	Hexamethylene diisocyanate
Cement workers	Potassium dichromate
Chrome platers, chrome polishers	Sodium bichromate, chromic acid, potassium chromate
Nickel platers	Nickel sulphate
Platinum chemists	Chloroplatinic acid
Platinum refiners	Platinum salts
Polyurethane foam manufacturers, printers, laminators	Diphenylmethane diisocyanate
Rubber workers	Naphthalene diisocyanate
Tungsten carbide grinders	Cobalt
Welders	Stainless steel fumes

Drugs and enzymes

Occupation	Agent
Ampicillin manufacturers	Phenylglycine acid chloride
Detergent manufacturers	Bacillus subtilis
Enzyme manufacturers	Fungal alpha-amylase
Food technologists, laboratory workers	Papain
Pharmacists	Gentian powder, flaviastase
Pharmaceutical workers	Methyldopa, salbutamol, dichloramine, piperazine dihydrochloride, spiramycin, penicillins, sulphathiazole, sulphonechloramides,

Occupation	Agent
Aircraft fitters	Triethyltetramine
Aluminum cable solderers	Aminoethylethanolamine
Aluminum pot room workers	Fluorine
Autobody workers	Acrylates (resins, glues, sealants, adhesives)
Brewery workers	Chloramine-T
Chemical plant workers, pulp mill workers	Chlorine
Dye weighers	Levafix brilliant yellow, drimarene brilliant yellow and blue, cibachrome brilliant scarlet
Electronics workers	Colophony
Epoxy resin manufacturers	Tetrachlorophthalic anhydride
Foundry mold makers	Furan-based resin binder systems
Fur dyers	Para-phenylenediamine
Hairdressers	Persulphate salts
Health care workers	Glutaraldehyde, latex
Laboratory workers, nurses, phenolic resin molders	Formaldehyde
Meat wrappers	Polyvinyl chloride vapour
Paint manufacturers, plastic molders, tool setters	Phthalic anhydride
Paint sprayers	Dimethylethanolamine
Photographic workers, shellac manufacturers	Ethylenediamine
	chloramine-T, phosdrin, pancreatic extracts
Poultry workers	Amprolium hydrochloride
Process workers, plastic polymer production workers	Trypsin, bromelin

Woods

Occupation	Agent
Carpenters, timber millers, woodworkers	Western red cedar, cedar of Lebanon, iroko, California redwood, ramin, African zebrawood
Sawmill workers, pattern makers	Mansonia, oak, mahogany, abiruana
Wood finishers	Cocabolla
Wood machinists	Kejaat

Refrigeration industry workers	CFCs
Solderers	Polyether alcohol, polypropylene glycol

Chapter 11

Beta$_2$-Adrenergic Agonist and Salmeterol

Beta$_2$-adrenergic agonist

β_2-adrenergic agonists, also known as **β_2-adrenergic receptor agonists**, are a class of drugs used to treat asthma and other pulmonary disease states.

Uses

They act on the beta$_2$-adrenergic receptor, thereby causing smooth muscle relaxation, resulting in dilation of bronchial passages, vasodilation in muscle and liver, relaxation of uterine muscle, and release of insulin. Side-effects such as insomnia, anxiety, and tremor occur in some patients. All β_2 agonists are available in inhaler form, either metered-dose inhalers, which aerosolize the drug, or dry powder, which can be inhaled.

Salbutamol (known as albuterol in the U.S.) also comes in a solution form for nebulization, which is more commonly used in inhalers than in emergency rooms. Salbutamol and terbutaline are also both available in oral forms. Nebuliser form is as effective as administering the drug intravenously.

In addition, several of these medications are available in intravenous forms, including both salbutamol and terbutaline. It can be used in this form in severe cases of asthma, but it is more commonly used to suppress premature labor because it also relaxes uterine muscle, thereby inhibiting contractions.

Risks

On November 18, 2005, Food and Drug Administration (FDA) alerted healthcare professionals and patients that several long-acting bronchodilator medicines have been associated with possible increased risk of worsening wheezing in some people, and requested that manufacturers update warnings in their existing product labeling.

On June 29, 2006, Cornell University and Stanford University researchers reported that a meta-analysis they conducted found that "regularly inhaled beta-agonists (Orciprenaline/metaproterenol [Alupent], formoterol Foradil, Fluticasone/salmeterol [Serevent, Advair], and Salbutamol/albuterol [Proventil, Ventolin, Volmax, and others])

increased the risk of respiratory death more than twofold, compared with a placebo," while used to treat chronic obstructive pulmonary disease (COPD).

On December 11, 2008, a panel of experts convened by the Food and Drug Administration (FDA) voted to ban the drugs Serevent and Foradil from use in the treatment of asthma. It was shown that, when these two drugs are used without steroids, they increase the risks of more severe attacks. The experts said that two other much more popular asthma drugs containing long-acting beta-agonists, Advair and Symbicort, should continue to be used. The latter contains formoterol as contained in Foradil but also a steroid Budesonide.

Types

They can be divided into short-acting and long-acting beta-adrenoceptor agonist (LABA) groups:

Short-acting beta$_2$ agonists

generic name (Trade Name)

- salbutamol (Albuterol (US name), Ventolin)
- levalbuterol
- terbutaline (Bricanyl)
- pirbuterol (Maxair)
- procaterol
- metaproterenol (Alupent)
- fenoterol
- bitolterol mesylate
- ritodrine

Long-acting beta$_2$ agonists

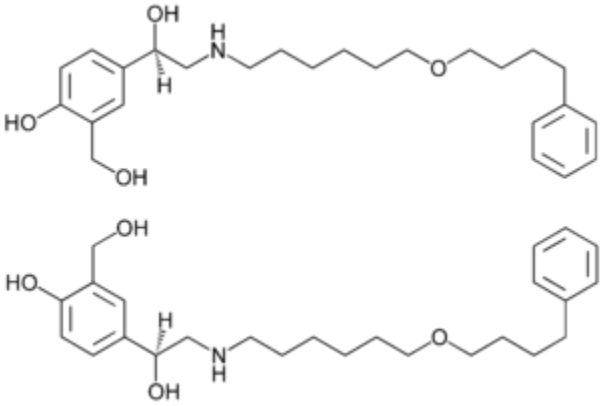
- salmeterol (Serevent Diskus)
- formoterol (Foradil)
- bambuterol
- clenbuterol

Ultra-long-acting beta$_2$ agonists

- indacaterol

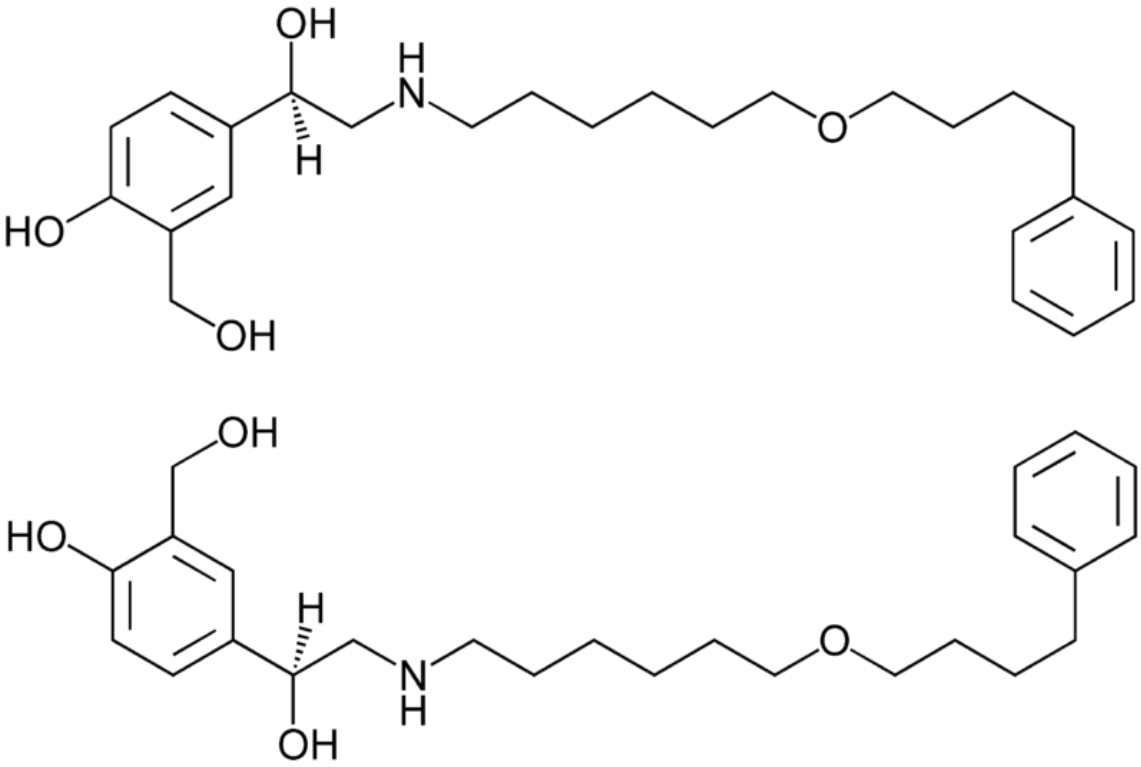
Salmeterol

Salmeterol



Systematic (IUPAC) name	
(*RS*)-2-(hydroxymethyl)-4-{1-hydroxy-2-[6-(4-phenylbutoxy) hexylamino]ethyl}phenol	
Identifiers	
CAS number	89365-50-4
ATC code	R03AC12
PubChem	CID 5152
IUPHAR ligand	559
DrugBank	APRD00277
ChemSpider	7987886 ✓
UNII	2I4BC502BT ✓
ChEMBL	CHEMBL1263 ✓
Chemical data	
Formula	$C_{25}H_{37}NO_4$
Mol. mass	415.57
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Protein binding	96%
Metabolism	hepatic CYP3A4
Half-life	5.5 h

Therapeutic considerations	
Pregnancy cat.	?
Legal status	Prescription Only (S4) (AU) POM (UK) ℞-only (US)
Routes	Inhalation



Salmeterol is a long-acting beta2-adrenergic receptor agonist drug that is currently prescribed for the treatment of asthma and chronic obstructive pulmonary disease (COPD). It is currently available as a proprietary "disk-styled" inhaler that releases a powdered form of the drug (dry powder inhaler). Until (31 December 2007) it was also available as a metered-dose inhaler (MDI).

Structure Activity Relationship

Salmeterol has an aryl alkyl group with a chain length of 11-atoms from the amine. This bulkiness makes the compound more lipophilic and it also makes it β receptor selective

Indications

It is a long-acting beta-adrenoceptor agonist (LABA), usually prescribed only for severe persistent asthma following previous treatment with a short-acting beta agonist such as salbutamol and is prescribed concurrently with a corticosteroid, such as beclomethasone.

The primary noticeable difference of salmeterol to salbutamol is that the duration of action lasts approximately 12 hours in comparison with 4–6 hours of salbutamol.

When used regularly every day as prescribed, inhaled salmeterol decreases the number and severity of asthma attacks. However, like all LABA medications, it is not for use for relieving an asthma attack that has already started.

Inhaled salmeterol works like other beta 2-agonists, causing bronchodilation by relaxing the smooth muscle in the airway so as to treat the exacerbation of asthma. The long duration of formoterol action occurs by the formoterol molecules initially diffusing into the plasma membrane of the lung cells, and then slowly being released back outside the cell where they can come into contact with the beta-2 adrenoceptors. Formoterol has been demonstrated to have a faster onset of action than salmeterol as a result of a lower lipophilicity, and has also been demonstrated to be more potent—a 12 μg dose of formoterol has been demonstrated to be equivalent to a 50 μg dose of salmeterol.

Formulations

Currently available long-acting $beta_2$-adrenoceptor agonists include salmeterol, formoterol, bambuterol, and sustained-release oral albuterol. Combinations of inhaled steroids and long-acting bronchodilators are becoming more widespread; the most common combination currently in use is fluticasone/salmeterol (**Advair** in the United States, **Seretide** in the UK).

History and concerns

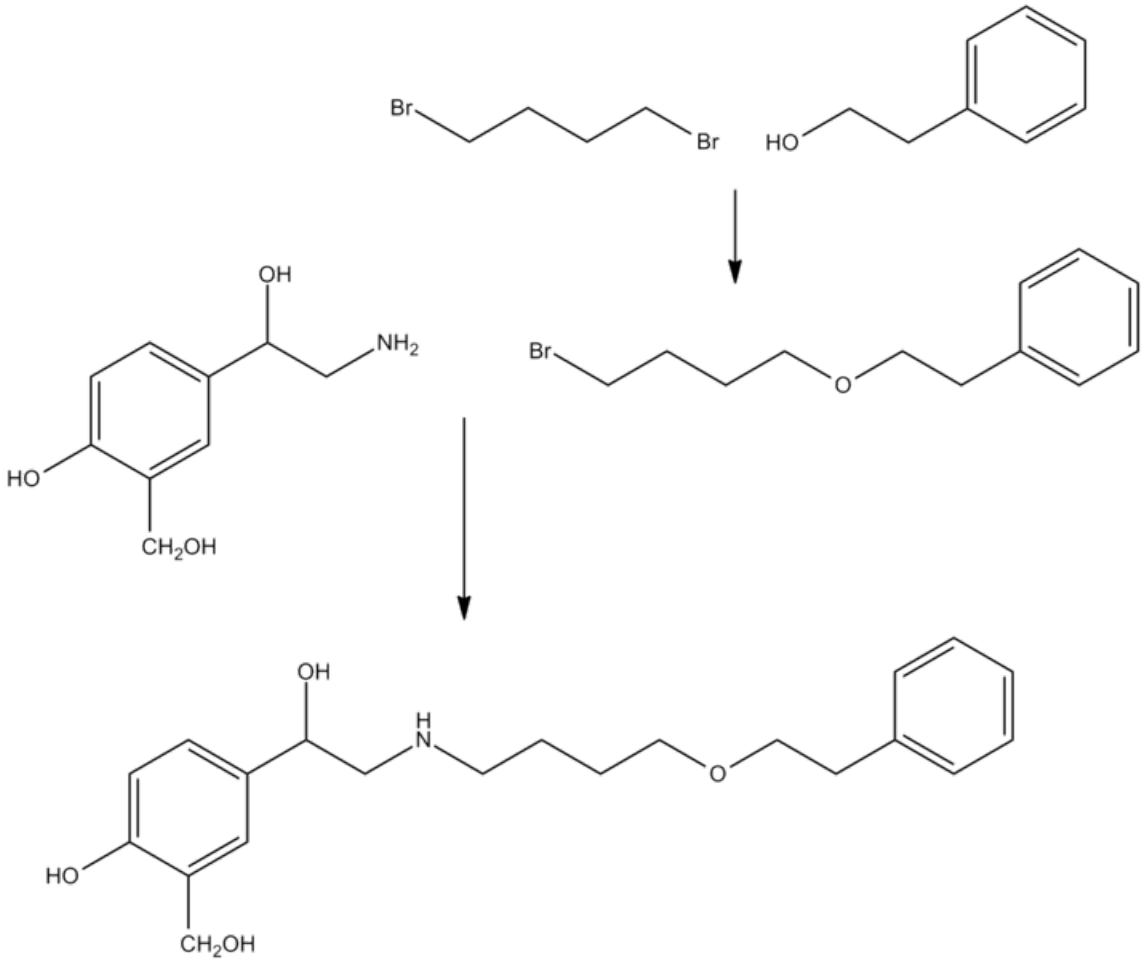
A typical inhaler, of Serevent (salmeterol) (no longer on market)

Salmeterol, marketed and manufactured by GlaxoSmithKline, in the 1980s and was released as Serevent in 1990. However, the product is under license from Allen & Hanburys.(UK)

In November 2005, the American FDA released a health advisory, alerting the public to findings that show the use of long-acting β_2-agonists could lead to a worsening of symptoms, and in some cases death.

While the use of inhaled LABAs are still recommended in asthma guidelines for the resulting improved symptom control, further concerns have been raised, by a large meta-analysis of the pooled results from 19 trials with 33,826 participants, that salmeterol may increase the small risks of asthma deaths, and this additional risk is not reduced with the additional use of inhaled steroids (e.g., as with the combination product Fluticasone/salmeterol). This seems to occur because although LABAs relieve asthma symptoms, they also promote bronchial inflammation and sensitivity without warning.

Synthesis



Skidmore, I. F.; Lunts, L. H. C.; Finch, H.; Naylor, A.; German Offen., 1984, 3414752; Chem. Abstr., 1986, 102, 95383.

Chapter 12

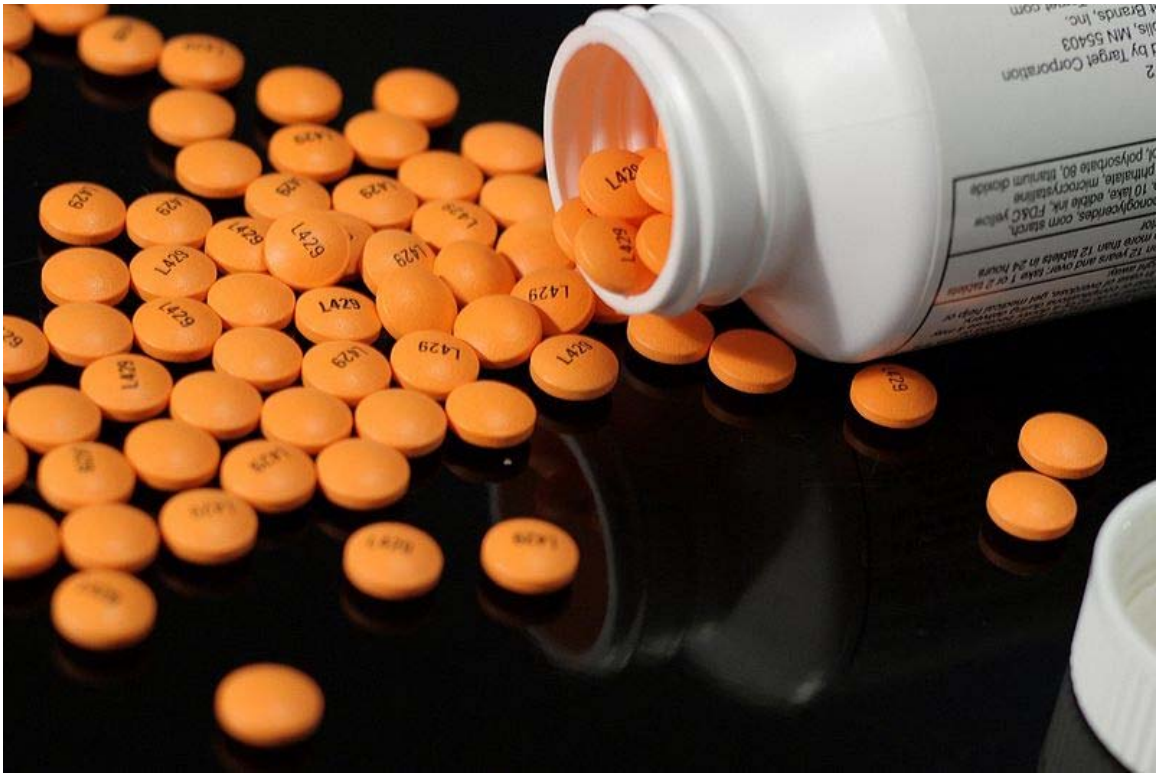
Aspirin-Induced Asthma and Exercise-Induced Asthma

Aspirin-induced asthma

Samter's triad

Aspirin in tablets

ICD-10	J45.1, J45.8
ICD-9	493.1
OMIM	208550
MeSH	D055963



Samter's triad is a medical condition consisting of asthma, aspirin sensitivity, and nasal/ethmoidal polyposis. It occurs in middle age (twenties and thirties are the most common onset times) and may not include any allergies.

Signs and symptoms

Most commonly, the first symptom is rhinitis (inflammation or irritation of the nasal mucosa), which can manifest with symptoms of sneezing, runny nose, or congestion. The disorder typically progresses to asthma, then polyposis, with aspirin sensitivity coming last. The aspirin reaction can be severe, including an asthma attack, anaphylaxis, and urticaria in some cases. Patients typically react to other NSAIDS such as ibuprofen, although paracetamol (known as acetaminophen in the United States) is generally considered safe.

Anosmia (lack of smell) is also typical, as the inflammation reaches the olfactory receptors in the nose.

Cause

The disorder is caused by an anomaly in the arachidonic acid cascade, which causes undue production of leukotrienes, a series of chemicals involved in the body's inflammatory response. When prostaglandin production is blocked by NSAIDS like aspirin, the cascade shunts entirely to leukotrienes, causing overproduction of LT-4 and producing the severe allergy-like effects.

There may be a relationship between aspirin-induced asthma and *TBX21*, *PTGER2*, and *LTC4S*.

Treatment

Medication

The preferred treatment now is desensitization to aspirin, undertaken at a clinic specializing in such treatment. Patients who are desensitized then take a maintenance dose of aspirin daily; they have reduced need for supporting medications and fewer asthma and sinusitis symptoms than previously; many have an improved sense of smell.

Treatment formerly focused on relieving the symptoms. Even desensitized people may continue to use nasal steroids, inhaled steroids, and leukotriene antagonists.

Leukotriene antagonists and inhibitors (montelukast, zafirlukast, and zileuton) are helpful in treating Samter's.

Some patients require oral steroids to alleviate asthma and congestion, and most patients will have recurring or chronic sinusitis due to the nasal inflammation. Desensitization reduces the chance of recurrence.

Surgery

Occasionally surgery may be required to remove polyps, although they typically recur, particularly if desensitization is not undertaken.

Diet

A diet low in omega-6 oils (precursors of arachidonic acid), and high in omega-3 oils, may also help.

Some people find relief of symptoms by following a low-salicylate diet such as the Feingold diet. They may need to eliminate the other salicylate-containing foods identified by Swain in 1985 as well. For those who need them, these salicylates are listed in charts in the Feingold Handbook based on level of salicylate measured in the item. Unfortunately, any such list is only a rough guideline since amounts will vary depending on fruit/vegetable variety and where grown; in fact, organic foods have been shown to contain more salicylate than conventional produce because the plant is more likely to be under attack from pests, and salicylate is produced by the plant as protection.

Alternate and related names

Samter's triad goes by several other names:

- Acetylsalicylic acid triad

- Widal's triad
- Francis' triad
- Aspirin triad

"AERD" ("aspirin-exacerbated respiratory disease") adds chronic rhinosinusitis to the triad. Similarly, "AIAR" ("aspirin-induced asthma and rhinitis") by definition includes rhinitis.

A sufferer who has not yet experienced asthma or aspirin sensitivity might be diagnosed as having:

- Non-allergic rhinitis
- Non-allergic rhinitis with eosinophilia syndrome (NARES)

History

It is named for Max Samter.

Initial reports on the link between asthma, aspirin and nasal polyposis were made by Widal in 1922. Further studies were done by Samter & Beers in reports published in 1968.

Exercise-induced asthma

Exercise-induced asthma	
ICD-9	493.81
DiseasesDB	31728
eMedicine	sports/155
MeSH	D001250

Exercise-induced asthma, or **E.I.A.**, is a medical condition characterized by shortness of breath induced by sustained aerobic exercise. It shares many features with other types of asthma, and responds to some typical asthma medications, but does not appear to be caused by the same inflammatory reaction as the other types.

Etiology

While the potential triggering events for E.I.A. are well delineated, the underlying pathogenesis is poorly understood. It usually occurs after at least several minutes of vigorous, "aerobic" activity, which demands that normal nasal breathing be supplemented by mouth-breathing. The resultant inhalation of air that has not been warmed and humidified by the nasal passages seems to generate increased blood flow to the linings of the bronchial tree, resulting in edema. Constriction of these vessels then follows, worsening the degree of obstruction to airflow. This sequence generates symptoms similar to those seen in other forms of asthma, but occurs without the inflammatory changes that underlie them.

Signs and symptoms

During an attack, the E.I.A. victim will likely be short of breath and/or coughing, with an elevated respiratory rate and wheezing, which may be audible even without a stethoscope. Examination will usually reveal the wheezing and a prolonged expiratory phase. In the occasional severe attack, altered level of consciousness and cyanosis due to depressed oxygenation of the blood may occur. Severe attacks are often the result of someone with both allergic and exercise-induced asthma exercising in a high-allergen environment (e.g. walking uphill alongside slowly moving traffic at dusk), and can be fatal.

In most cases, a relative "refractory period" follows resolution of an attack. During this approximately one hour period, resumption of exercise will likely produce either none or mild symptoms. Curiously as well, some 6–10 hours after the initial attack, a rebound attack with milder symptoms often develops without precipitating exertion.

Treatment

As with any asthma, the best treatment is avoidance, when possible, of conditions predisposing to attacks. In athletes who wish to continue their sport, or do so at times in adverse conditions, preventive measures, including altered training techniques and medications, can be taken.

Some athletes take advantage of the refractory period by precipitating an attack by "warming up," and then timing their competition such that it occurs during the refractory period. Step-wise training works in a similar fashion. An athlete warms up in stages of increasing intensity, using the refractory period generated by each stage to get up to a full workload.

The most common medication approach is to use a beta agonist about twenty minutes before exercise. Some physicians prescribe inhaled anti-inflammatory mists such as corticosteroids or leukotriene antagonists, and mast cell stabilizers have also proven effective. A randomized crossover study compared oral montelukast with inhaled

salmeterol, both given two hours before exercise. Both drugs had similar benefit but montelukast lasted 24 hours.

Prognosis

As evidenced by the many professional athletes who have overcome E.I.A. using some combination of the above treatments, the prognosis is usually very good. Olympic swimmers Tom Dolan, Amy Van Dyken, and Nancy Hogshead, Olympic track star Jackie Joyner-Kersee, baseball Hall of Famer Catfish Hunter, and American football player Jerome Bettis are among the many who have done so.

According to International Olympic Committee statistics, during most of Olympic Games in last 20 years from 1/3 to 2/3 of athletes claimed to have asthma. Some medical experts tie such inordinate rates of reported asthma with athletes' desire to use complex medication to help them achieve better results.

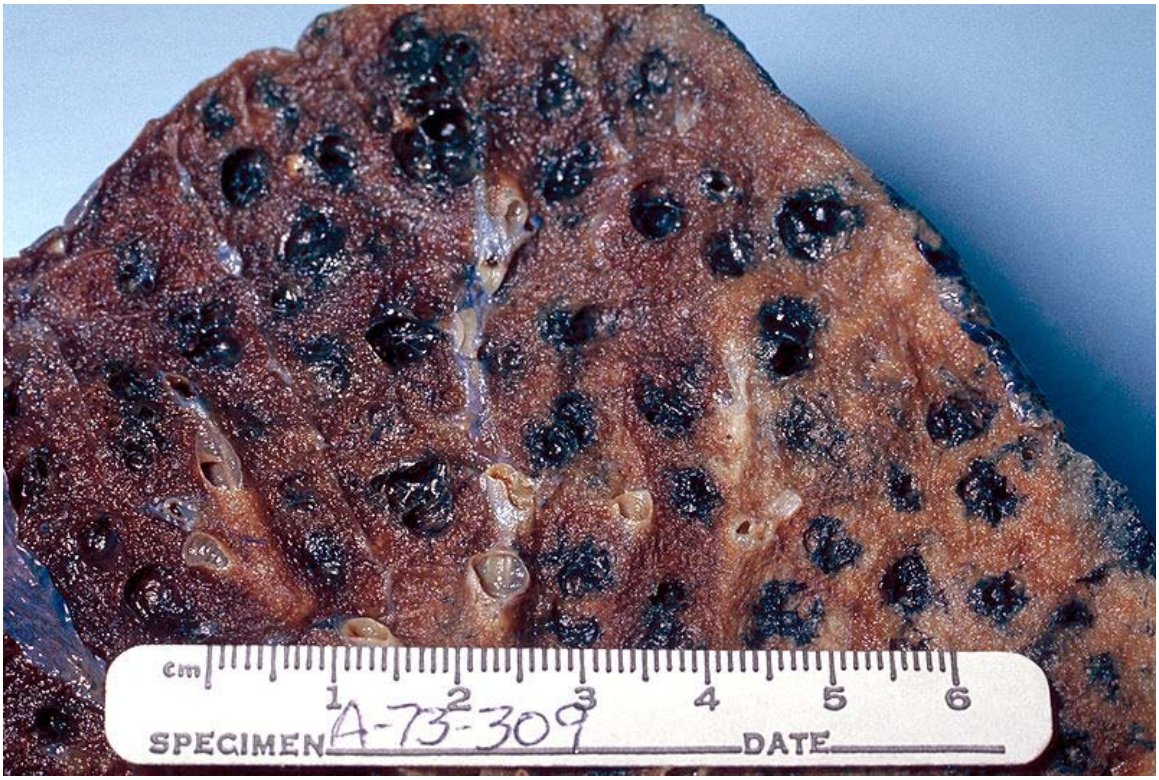
Chapter 13

Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease

Gross pathology of a lung showing centrilobular-type emphysema characteristic of smoking. This close-up of the fixed, cut lung surface shows multiple cavities lined by heavy black carbon deposits.

ICD-10	J40. - J44., J47.
ICD-9	490 - 492, 494 - 496
OMIM	606963
DiseasesDB	2672
MedlinePlus	000091
eMedicine	med/373 emerg/99
MeSH	*C08.381.495.389*



Chronic obstructive pulmonary disease (**COPD**), also known as **chronic obstructive lung disease** (**COLD**), **chronic obstructive airway disease** (**COAD**), **chronic airflow limitation** (**CAL**) and **chronic obstructive respiratory disease** (**CORD**), refers to chronic bronchitis and emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs causing shortness of breath. In clinical practice, COPD is defined by its characteristically low airflow on lung function tests. In contrast to asthma, this limitation is poorly reversible and usually gets progressively worse over time. In England, an estimated 842,100 of 50 million people have a diagnosis of COPD; translating into approximately one person in 59 receiving a diagnosis of COPD at some point in their lives.

COPD is caused by noxious particles or gas, most commonly from tobacco smoking, which triggers an abnormal inflammatory response in the lung. The inflammatory response in the larger airways is known as chronic bronchitis, which is diagnosed clinically when people regularly cough up sputum. In the alveoli, the inflammatory response causes destruction of the tissues of the lung, a process known as emphysema. The natural course of COPD is characterized by occasional sudden worsenings of symptoms called acute exacerbations, most of which are caused by infections or air pollution.

The diagnosis of COPD requires lung function tests. Important management strategies are smoking cessation, vaccinations, rehabilitation, and drug therapy (often using inhalers). Some patients go on to require long-term oxygen therapy or lung transplantation.

Worldwide, COPD ranked as the sixth leading cause of death in 1990. It is projected to be the fourth leading cause of death worldwide by 2030 due to an increase in smoking rates and demographic changes in many countries. COPD is the fourth leading cause of death in the U.S. and the economic burden of COPD in the U.S. in 2007 was $42.6 billion in health care costs and lost productivity.

Classification

The twofold nature of the pathology has been studied in the past. Furthermore, also in recent studies, many authors found that each patient could be classified as presenting a predominantly bronchial or emphysematous phenotype simply analyzing clinical, functional, and radiological findings or studying interesting biomarkers. A statistical model reflecting the specific predominant mechanism of airflow limitation for a specific patient has been developed and trained over a database of hundreds of patients.

Chronic bronchitis

Lung damage and inflammation in the large airways results in chronic bronchitis. Chronic bronchitis is defined in clinical terms as a cough with sputum production on most days for 3 months of a year, for 2 consecutive years. In the airways of the lung, the hallmark of chronic bronchitis is an increased number (hyperplasia) and increased size (hypertrophy) of the goblet cells and mucous glands of the airway. As a result, there is more mucus than usual in the airways, contributing to narrowing of the airways and causing a cough with sputum. Microscopically there is infiltration of the airway walls with inflammatory cells. Inflammation is followed by scarring and remodeling that thickens the walls and also results in narrowing of the airways. As chronic bronchitis progresses, there is squamous metaplasia (an abnormal change in the tissue lining the inside of the airway) and fibrosis (further thickening and scarring of the airway wall). The consequence of these changes is a limitation of airflow.

Patients with advanced COPD that have primarily chronic bronchitis rather than emphysema were commonly referred to as "blue bloaters" because of the bluish color of the skin and lips (cyanosis) seen in them. The hypoxia and fluid retention leads to them being called "Blue Bloaters."

Emphysema

Lung damage and inflammation of the air sacs (alveoli) results in emphysema. Emphysema is defined as enlargement of the air spaces distal to the terminal bronchioles, with destruction of their walls. The destruction of air space walls reduces the surface area available for the exchange of oxygen and carbon dioxide during breathing. It also reduces the elasticity of the lung itself, which results in a loss of support for the airways that are embedded in the lung. These airways are more likely to collapse causing further limitation to airflow. The effort made by patients suffering from emphysema during exhalation, causes a pink color in their faces, hence the term commonly used to refer to them, "pink puffers".

Signs and symptoms

Essentials of diagnosis include:

- History of cigarette smoking.
- Chronic cough and sputum production (in chronic bronchitis)
- Dyspnea (in emphysema)
- Rhonchi, decreased intensity of breath sounds, and prolonged expiration on physical examination
- Airflow limitation on pulmonary function testing that is not fully reversible and most often progressive

One of the most common symptoms of COPD is shortness of breath (dyspnea). People with COPD commonly describe this as: "My breathing requires effort," "I feel out of breath," or "I can't get enough air in". People with COPD typically first notice dyspnea during vigorous exercise when the demands on the lungs are greatest. Over the years, dyspnea tends to get gradually worse so that it can occur during milder, everyday activities such as housework. In the advanced stages of COPD, dyspnea can become so bad that it occurs during rest and is constantly present.

Other symptoms of COPD are a persistent cough, sputum or mucus production, wheezing, chest tightness, and tiredness.

People with advanced (very severe) COPD sometimes develop respiratory failure. When this happens, cyanosis, a bluish discoloration of the lips caused by a lack of oxygen in the blood, can occur. An excess of carbon dioxide in the blood can cause headaches, drowsiness or twitching (asterixis). A complication of advanced COPD is cor pulmonale, a strain on the heart due to the extra work required by the heart to pump blood through the affected lungs. Symptoms of cor pulmonale are peripheral edema, seen as swelling of the ankles, and dyspnea.

There are a few signs of COPD that a healthcare worker may detect although they can be seen in other diseases. Some people have COPD and have none of these signs. Common signs are:

- tachypnea, a rapid breathing rate
- wheezing sounds or crackles in the lungs heard through a stethoscope
- breathing out taking a longer time than breathing in
- enlargement of the chest, particularly the front-to-back distance (hyperaeration)
- active use of muscles in the neck to help with breathing
- breathing through pursed lips
- increased anteroposterior to lateral ratio of the chest (i.e. barrel chest).

Cause

Smoking

The primary risk factor for COPD is chronic tobacco smoking. In the United States, 80 to 90% of cases of COPD are due to smoking. Exposure to cigarette smoke is measured in pack-years, the average number of packages of cigarettes smoked daily multiplied by the number of years of smoking. The likelihood of developing COPD increases with age and cumulative smoke exposure, and almost all life-long smokers will develop COPD, provided that smoking-related, extrapulmonary diseases (cardiovascular, diabetes, cancer) do not claim their lives beforehand.

Occupational exposures

Intense and prolonged exposure to workplace dusts found in coal mining, gold mining, and the cotton textile industry and chemicals such as cadmium, isocyanates, and fumes from welding have been implicated in the development of airflow obstruction, even in nonsmokers. Workers who smoke and are exposed to these particles and gases are even more likely to develop COPD. Intense silica dust exposure causes silicosis, a restrictive lung disease distinct from COPD; however, less intense silica dust exposures have been linked to a COPD-like condition. The effect of occupational pollutants on the lungs appears to be substantially less important than the effect of cigarette smoking.

Air pollution

Studies in many countries have found that people who live in large cities have a higher rate of COPD compared to people who live in rural areas. Urban air pollution may be a contributing factor for COPD as it is thought to slow the normal growth of the lungs although the long-term research needed to confirm the link has not been done and would help understanding of the condition although studies of the industrial waste gas and COPD/Asthma aggravating compound Sulphur Dioxide and the inverse relation to the presence of the blue Lychen Xanthoria (usually found abundantly in the countryside, but never in towns or cities) have been seen to suggest that combustive industrial processes do not aid COPD sufferers. In many developing countries indoor air pollution from cooking fire smoke (often using biomass fuels such as wood and animal dung) is a common cause of COPD, especially in women.

Genetics

Some factor in addition to heavy smoke exposure is required for a person to develop COPD. This factor is probably a genetic susceptibility. COPD is more common among relatives of COPD patients who smoke than unrelated smokers. The genetic differences that make some peoples' lungs susceptible to the effects of tobacco smoke are mostly unknown. Alpha 1-antitrypsin deficiency is a genetic condition that is responsible for about 2% of cases of COPD. In this condition, the body does not make enough of a protein, alpha 1-antitrypsin. Alpha 1-antitrypsin protects the lungs from damage caused

by protease enzymes, such as elastase and trypsin, that can be released as a result of an inflammatory response to tobacco smoke.

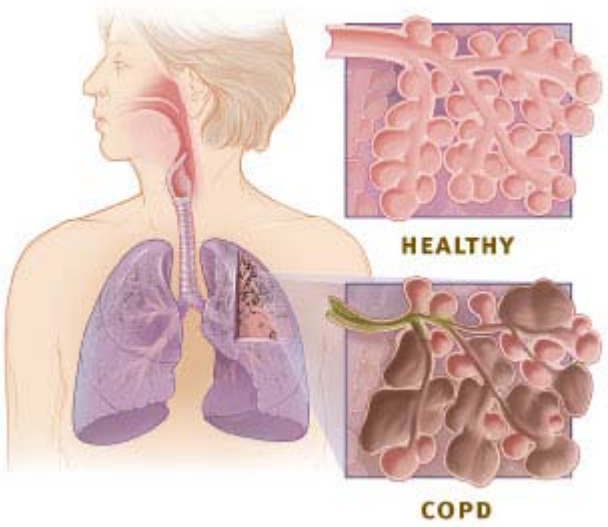
Other risk factors

A tendency to sudden airway constriction in response to inhaled irritants, bronchial hyperresponsiveness, is a characteristic of asthma. Many people with COPD also have this tendency. In COPD, the presence of bronchial hyperresponsiveness predicts a worse course of the disease. It is not known if bronchial hyperresponsiveness is a cause or a consequence of COPD. Other risk factors such as repeated lung infection and possibly a diet high in cured meats (possibly due to the preservative sodium nitrite) may be related to the development of COPD.

Autoimmune disease

There is mounting evidence that there may be an autoimmune component to COPD, triggered by lifelong smoking. Many individuals with COPD who have stopped smoking have active inflammation in the lungs. The disease may continue to get worse for many years after stopping smoking due to this ongoing inflammation. This sustained inflammation is thought to be mediated by autoantibodies and autoreactive T cells.

Pathophysiology

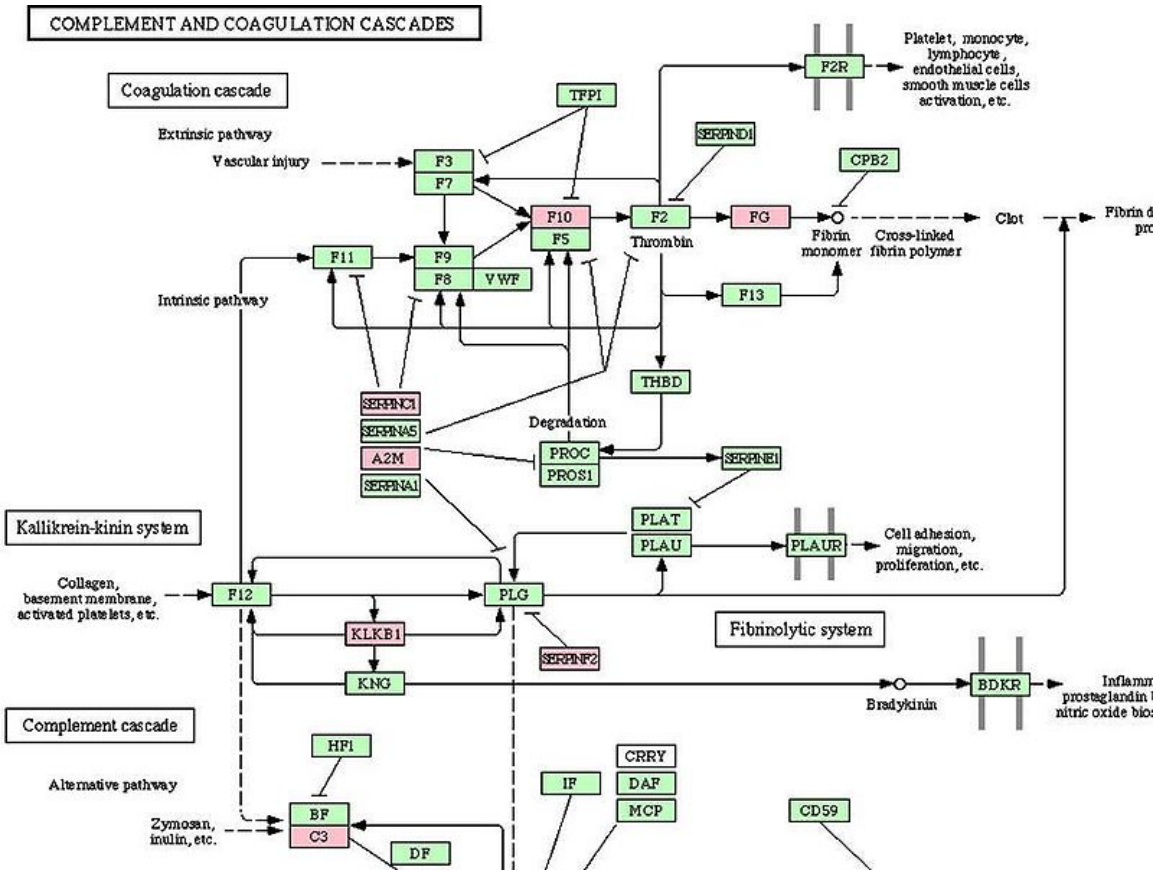


Enlarged view of lung tissue showing the difference between healthy lung and COPD

It is not fully understood how tobacco smoke and other inhaled particles damage the lungs to cause COPD. The most important processes causing lung damage are:

- Oxidative stress produced by the high concentrations of free radicals in tobacco smoke.

- Cytokine release due to inflammation as the body responds to irritant particles such as tobacco smoke in the airway.
- Tobacco smoke and free radicals impair the activity of antiprotease enzymes such as alpha 1-antitrypsin, allowing protease enzymes to damage the lung.



Potential role of Coagulation and the Complement System in COPD; a complex cascade of blood plasma proteins and platelet activation as molecular perturbations associated with patients suffering from Chronic Obstructive Pulmonary Disease.

Narrowing of the airways reduces the rate at which air can flow to and from the air sacs (alveoli) and limits the effectiveness of the lungs. In COPD, the greatest reduction in air flow occurs when breathing out (during expiration) because the pressure in the chest tends to compress rather than expand the airways. In theory, air flow could be increased by breathing more forcefully, increasing the pressure in the chest during expiration. In COPD, there is often a limit to how much this can actually increase air flow, a situation known as expiratory flow limitation.

If the rate of airflow is too low, a person with COPD may not be able to completely finish breathing out (expiration) before he or she needs to take another breath. This is particularly common during exercise when breathing has to be faster. A little of the air of the previous breath remains within the lungs when the next breath is started. When this

happens, there is an increase in the volume of air in the lungs, a process called dynamic hyperinflation.

Dynamic hyperinflation is closely linked to shortness of breath (dyspnea) in COPD. It is less comfortable to breathe with hyperinflation because it takes more effort to move the lungs and chest wall when they are already stretched by hyperinflation.

Another factor contributing to shortness of breath in COPD is the loss of the surface area available for the exchange of oxygen and carbon dioxide with emphysema. This reduces the rate of transfer of these gasses between the body and the atmosphere and can lead to low oxygen and high carbon dioxide levels in the body. A person with emphysema may have to breathe faster or more deeply to compensate, which can be difficult to do if there is also flow limitation or hyperinflation.

Some people with advanced COPD do manage to breathe fast to compensate, but usually have dyspnea as a result. Others, who may be less short of breath, tolerate low oxygen and high carbon dioxide levels in their bodies but this can eventually lead to headaches, drowsiness and heart failure.

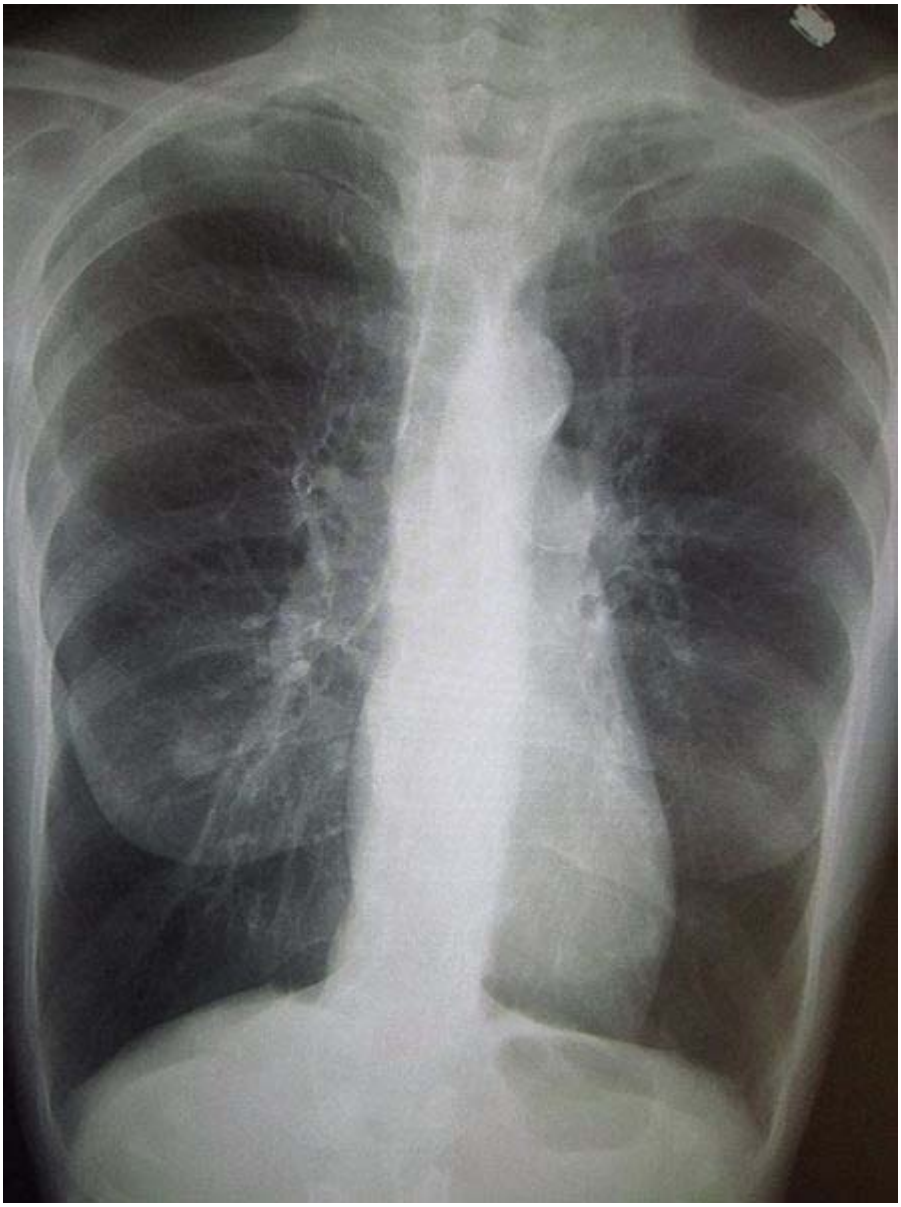
Advanced COPD can lead to complications beyond the lungs such as weight loss (cachexia), pulmonary hypertension and right-sided heart failure (cor pulmonale). Osteoporosis, heart disease, muscle wasting and depression are all more common in people with COPD.

Several molecular signatures associated to lung function decline and corollaries of disease severity have been proposed, a majority of which are characterized in easily accessible surrogate tissue, including blood derivatives such as serum and plasma. A recent 2010 clinical study proposes alpha 1B-glycoprotein precursor/A1BG, Alpha 2-antiplasmin, apolipoprotein A-IV precursor/APOA4, and complement component 3 precursor, among other coagulation and complement system proteins as corrollaries of lung function decline, although ambiguity between cause and effect is unresolved.

Acute exacerbations of COPD

An acute exacerbation of COPD is a sudden worsening of COPD symptoms (shortness of breath, quantity and color of phlegm) that typically lasts for several days. It may be triggered by an infection with bacteria or viruses or by environmental pollutants. Typically, infections cause 75% or more of the exacerbations; bacteria can roughly be found in 25% of cases, viruses in another 25%, and both viruses and bacteria in another 25%. Pulmonary Embolism can also cause exacerbations of COPD. Airway inflammation is increased during the exacerbation resulting in increased hyperinflation, reduced expiratory air flow and worsening of gas transfer. This can also lead to hypo ventilation and eventually hypoxia, thus can lead to insufficient tissue perfusion then cell necrosis.

Diagnosis



A chest X-ray demonstrating severe COPD. Note the small size of the heart in comparison to the lungs.

The diagnosis of COPD should be considered in anyone who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease such as regular tobacco smoking. No single symptom or sign can adequately confirm or exclude the diagnosis of COPD although COPD is uncommon under the age of 40 years.

Spirometry

The diagnosis of COPD is confirmed by spirometry, a test that measures breathing. Spirometry measures the forced expiratory volume in one second (FEV_1) which is the greatest volume of air that can be breathed out in the first second of a large breath. Spirometry also measures the forced vital capacity (FVC) which is the greatest volume of air that can be breathed out in a whole large breath. Normally at least 70% of the FVC comes out in the first second (i.e. the FEV_1/FVC ratio is >70%). A ratio of less than normal defines the patient as having COPD. More specifically, the diagnosis of COPD is made when the FEV_1/FVC ratio is <70%. The GOLD criteria also requires that values are after bronchodilator medication has been given to make the diagnosis, and the NICE criteria also requires FEV1%. According to the ERS criteria, it is FEV1% predicted that defines when a patient has COPD, that is, when FEV1% predicted is < 88% pred for men, or < 89% for women.

Spirometry can help to determine the severity of COPD. The FEV_1 (measured post-bronchodilator) is expressed as a percent of a predicted "normal" value based on a person's age, gender, height and weight:

Severity of COPD	FEV_1 % predicted
Mild	≥80
Moderate	50–79
Severe	30–49
Very severe	<30 or Chronic respiratory failure symptoms

The severity of COPD also depends on the severity of dyspnea and exercise limitation. These and other factors can be combined with spirometry results to obtain a COPD severity score that takes multiple dimensions of the disease into account.

Other tests

On chest x-ray the classic signs of COPD are over-expanded lung (hyperinflation), a flattened diaphragm, increased retrosternal airspace, and bullae. It can be useful to help exclude other lung diseases such as pneumonia, pulmonary edema or a pneumothorax. Complete pulmonary function tests with measurements of lung volumes and gas transfer may also show hyperinflation and can discriminate between COPD with emphysema and COPD without emphysema. A high-resolution computed tomography scan of the chest may show the distribution of emphysema throughout the lungs and can also be useful to exclude other lung diseases.

A blood sample taken from an artery can be tested for blood gas levels which may show low oxygen levels (hypoxemia) and/or high carbon dioxide levels (respiratory acidosis). A blood sample taken from a vein may show a high blood count (reactive polycythemia), a reaction to long-term hypoxemia.

Management

There is currently no cure for COPD; however, COPD is both a preventable and treatable disease. Clinical practice guidelines for the management of COPD are available from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a collaboration that includes the World Health Organization and the U.S. National Heart, Lung, and Blood Institute. The major current directions of COPD management are to assess and monitor the disease, reduce the risk factors, manage stable COPD, prevent and treat acute exacerbations and manage comorbidity.

The only measures that have been shown to reduce mortality is smoking cessation and supplemental oxygen.

Risk factor reduction

Smoking cessation

Smoking cessation is one of the most important factors in slowing down the progression of COPD. Once COPD has been diagnosed, stopping smoking slows down the rate of progression of the disease. Even at a late stage of the disease it can significantly reduce the rate of deterioration in lung function and delay the onset of disability and death. It is the only standard intervention that can improve the rate of progression of COPD.

Smoking cessation starts with an individual decision to stop smoking that leads to an attempt at quitting. Often several attempts are required before long-term smoking cessation is achieved. Some smokers can achieve long-term smoking cessation through "willpower" alone. However smoking is highly addictive and many smokers need further support to quit. The chance of successfully stopping smoking can be greatly improved through social support, engagement in a smoking cessation programme and the use of drugs such as nicotine replacement therapy, bupropion and varenicline.

The policies of governments, public health agencies and anti-smoking organizations can reduce smoking rates by encouraging smoking cessation and discouraging people from starting smoking. These policies are important strategies in the prevention of COPD.

Occupational health

Measures can be taken to reduce the likelihood that workers in at-risk industries such as coal mining will develop COPD. Some examples of these measures are: education of workers and management about the risks, promoting smoking cessation, surveillance of workers for early signs of COPD, the use of personal dust monitors, the use of respirators and dust control. Dust control can be achieved by improving ventilation, using water sprays and by using mining techniques that minimize dust generation. If a worker develops COPD, further lung damage can be reduced by avoiding ongoing dust exposure, for example by changing the work role.

Air pollution

Air quality can be improved by pollution reduction efforts which should lead to health gains for people with COPD. A person who has COPD may experience fewer symptoms if they stay indoors on days when air quality is poor.

Bronchodilators

Bronchodilators are medicines that relax smooth muscle around the airways, increasing the calibre of the airways and improving air flow. They can reduce the symptoms of shortness of breath, wheeze and exercise limitation, resulting in an improved quality of life for people with COPD. They do not slow down the rate of progression of the underlying disease. Bronchodilators are usually administered with an inhaler or via a nebulizer.

There are two major types of bronchodilator, β_2 agonists and anticholinergics. Anticholinergics appear to be superior to β_2 agonists in COPD. Anticholinergics reduce respiratory deaths while β_2 agonists have no effect on respiratory deaths. Each type may be either long-acting (with an effect lasting 12 hours or more) or short-acting (with a rapid onset of effect that does not last as long).

β_2 agonists

β_2 agonists stimulate β_2 receptors on airway smooth muscles, causing them to relax. There are several β_2 agonists available. Albuterol (common brand name: Ventolin) and terbutaline are widely used short acting β_2 agonists and provide rapid relief of COPD symptoms. Long acting β_2 agonists (LABAs) such as salmeterol and formoterol are used as maintenance therapy and lead to improved airflow, exercise capacity, and quality of life.

Anticholinergics

Anticholinergic drugs cause airway smooth muscles to relax by blocking stimulation from cholinergic nerves. Ipratropium is the most widely prescribed short acting anticholinergic drug. Like short-acting β_2 agonists, short-acting anticholinergics provide rapid relief of COPD symptoms and a combination of the two is commonly used for a greater bronchodilator effect. Tiotropium is the most commonly prescribed long-acting anticholinergic drug in COPD. It has more specificity for M_3 muscarinic receptors so may have fewer side-effects than other anticholinergic drugs. Regular use is associated with improvements in airflow, exercise capacity, quality of life and possibly a longer life. In January 2010, new research showed that ipratropium used to treat COPD increased cardiovascular morbidity. At the same time Tiotropium was shown to be effective in eliminating the risk of all cause mortality, cardiovascular mortality and cardiovascular events.

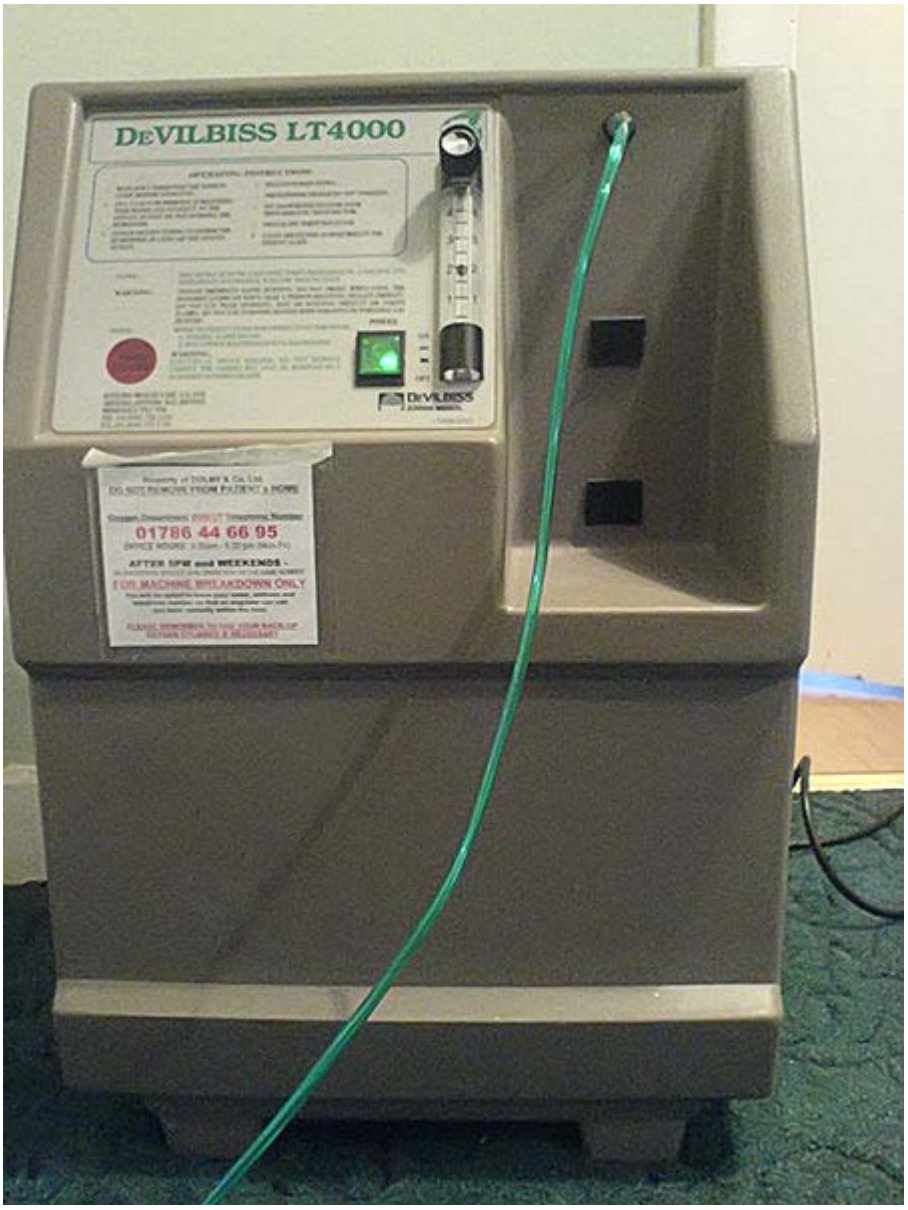
Corticosteroids

Corticosteroids act to reduce the inflammation in the airways, in theory reducing lung damage and airway narrowing caused by inflammation. Unlike bronchodilators, they do not act directly on the airway smooth muscle and do not provide immediate relief of symptoms. Some of the more common corticosteroids in use are prednisone, fluticasone, budesonide, mometasone, and beclomethasone. Corticosteroids are used in tablet or inhaled form to treat and prevent acute exacerbations of COPD. Well-inhaled corticosteroids (ICS) have not been shown to be of benefit for people with mild COPD, however, they have been shown to decrease acute exacerbations in those with either moderate or severe COPD. They however have no effect on overall one-year mortality and are associated with increased rates of pneumonia.

Other medication

Theophylline is a bronchodilator and phosphodiesterase inhibitor that in high doses can reduce symptoms for some people who have COPD. More often, side effects such as nausea and stimulation of the heart limit its use. In lower doses, it may slightly reduce the number of COPD exacerbations. The investigative phosphodiesterase-4 antagonists, roflumilast and cilomilast have completed Phase-2 clinical trials. Tumor necrosis factor antagonists such as infliximab suppress the immune system and reduce inflammation. Infliximab has been trialled in COPD but there was no evidence of benefit with the possibility of harm.

Supplemental oxygen



Oxygen can be delivered in different forms: in large containers, in smaller containers with liquid oxygen, or with the use of a oxygen concentrator (*shown here*) which derives oxygen from room air. The latter two options improve mobility of people requiring long-term oxygen therapy.

Supplemental oxygen can be given to people with COPD who have low oxygen levels in the body. Oxygen is provided from an oxygen cylinder or an oxygen concentrator and delivered to a person through tubing via a nasal cannula or oxygen mask. Supplemental oxygen does not greatly improve shortness of breath but can allow people with COPD and low oxygen levels to do more exercise and household activity. Long-term oxygen therapy for at least 16 hours a day can improve the quality of life and survival for people

with COPD and arterial hypoxemia or with complications of hypoxemia such as pulmonary hypertension, cor pulmonale, or secondary erythrocytosis. High concentrations of supplemental oxygen can lead to the accumulation of carbon dioxide and respiratory acidosis for some people with severe COPD; lower oxygen flow rates are generally safer for these individuals.

Pulmonary rehabilitation

Pulmonary rehabilitation is a program of exercise, disease management and counselling coordinated to benefit the individual. Pulmonary rehabilitation has been shown to improve shortness of breath and exercise capacity. It has also been shown to improve the sense of control a patient has over their disease as well as their emotions.

Nutrition

Being either underweight or overweight can affect the symptoms, degree of disability and prognosis of COPD. People with COPD who are underweight can improve their breathing muscle strength by increasing their calorie intake. When combined with regular exercise or a pulmonary rehabilitation programme, this can lead to improvements in COPD symptoms.

Surgery

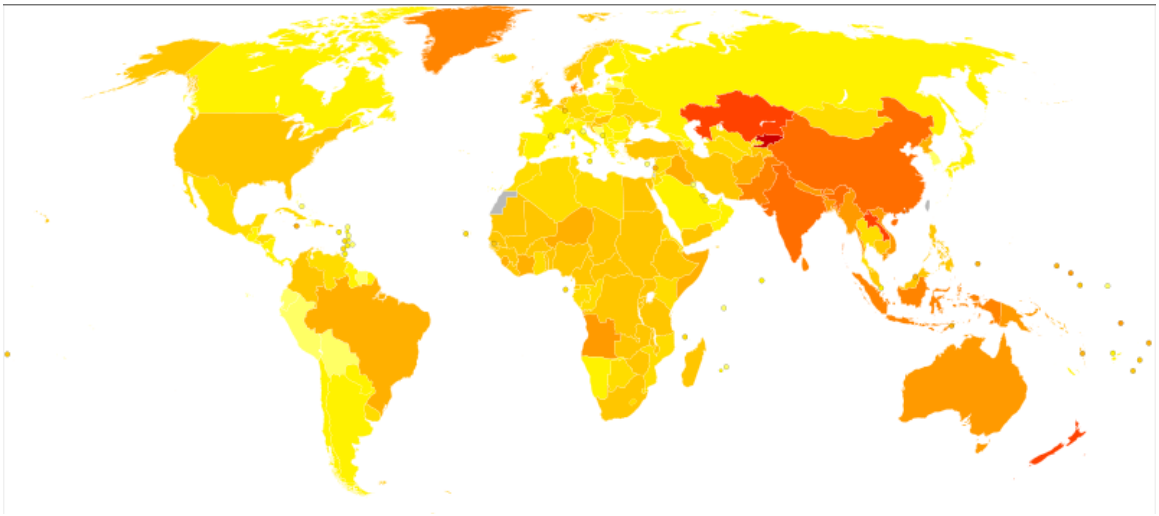
Surgery is sometimes helpful for COPD in selected cases. A bullectomy is the surgical removal of a bulla, a large air-filled space that can squash the surrounding, more normal lung. Lung volume reduction surgery is similar; parts of the lung that are particularly damaged by emphysema are removed allowing the remaining, relatively good lung to expand and work better. Lung transplantation is sometimes performed for severe COPD, particularly in younger individuals.

Prognosis

COPD usually gradually gets worse over time and can lead to death. The rate at which it gets worse varies between individuals. The factors that predict a poorer prognosis are:

- Severe airflow obstruction (low FEV_1)
- Poor exercise capacity
- Shortness of breath
- Significantly underweight or overweight
- Complications like respiratory failure or cor pulmonale
- Continued smoking
- Frequent acute exacerbations

Epidemiology



Disability-adjusted life year for chronic obstructive pulmonary disease per 100,000 inhabitants in 2004

- no data
- less than 110
- 110-220
- 220-330
- 330-440
- 440-550
- 550-660
- 660-770
- 770-880
- 880-990
- 990-1100
- 1100-1350
- more than 1350

COPD occurs in 34 out of 1000 greater than 65 years old. In England, an estimated 842,100 of 50 million people have a diagnosis of COPD; translating into approximately one person in 59 receiving a diagnosis of COPD at some point in their lives. In the most socioeconomically deprived parts of the country, one in 32 people were diagnosed with COPD, compared with one in 98 in the most affluent areas. In the United States, the prevalence of COPD is approximately 1 in 20 or 5%, totalling approximately 13.5 million people in USA, or possibly approximately 25 million people if undiagnosed cases are included.

History

COPD has probably always existed but has been called by different names in the past. Bonet described a condition of "voluminous lungs" in 1679. In 1769, Giovanni Morgagni described 19 cases where the lungs were "turgid" particularly from air. The first

description and illustration of the enlarged airspaces in emphysema was provided by Ruysh in 1721. Badham used the word "catarrh" to describe the cough and mucus hypersecretion of chronic bronchitis in 1814. He recognised that chronic bronchitis was a disabling disorder.

René Laennec, the physician who invented the stethoscope, used the term "emphysema" in his book *A Treatise on the Diseases of the Chest and of Mediate Auscultation* (1837) to describe lungs that did not collapse when he opened the chest during an autopsy. He noted that they did not collapse as usual because they were full of air and the airways were filled with mucus.

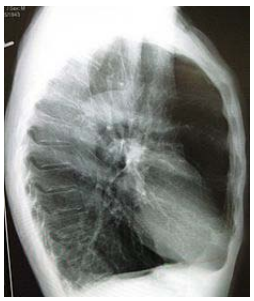
In 1842, John Hutchinson invented the spirometer, which allowed the measurement of vital capacity of the lungs. However, his spirometer could only measure volume, not airflow. Tiffeneau in 1947 and Gaensler in 1950 and 1951 described the principles of measuring airflow.

The terms chronic bronchitis and emphysema were formally defined at the CIBA guest symposium of physicians in 1959. The term COPD was first used by William Briscoe in 1965 and has gradually overtaken other terms to become established today as the preferred name for this disease.

Chapter 14

Emphysema

Emphysema



A lateral chest x-ray of a person with emphysema. Note the barrel chest and flat diaphragm.

ICD-10	J43.
ICD-9	492
DiseasesDB	4190
MedlinePlus	000136
eMedicine	med/654
MeSH	D011656

Emphysema is a long-term, progressive disease of the lungs that primarily causes shortness of breath. In people with emphysema, the tissues necessary to support the physical shape and function of the lungs are destroyed. It is included in a group of diseases called chronic obstructive pulmonary disease or COPD (pulmonary refers to the lungs). Emphysema is called an obstructive lung disease because the destruction of lung tissue around smaller sacs, called alveoli, makes these air sacs unable to hold their functional shape upon exhalation. It is often caused by smoking.

The term means *swelling* and comes from the Greek ἐμφυσᾶν *emhysan* meaning *inflate*, itself composed of ἐν *en* meaning *in* and φυσᾶν *physan* meaning *breath, blast*.

Classification

Emphysema can be classified into primary and secondary. However, it is more commonly classified by location into panacinary and centroacinary (or panacinar and centriacinar, or centrilobular and panlobular).

- *Panacinar* (or *panlobular*) emphysema: The entire respiratory acinus, from respiratory bronchiole to alveoli, is expanded. Occurs more commonly in the lower lobes, especially basal segments, and anterior margins of the lungs.
- *Centriacinar* (or *centrilobular*) emphysema: The respiratory bronchiole (proximal and central part of the acinus) is expanded. The distal acinus or alveoli are unchanged. Occurs more commonly in the upper lobes.

Other types include distal acinar and irregular. A special type is *congenital lobar emphysema (CLE)*.

Congenital lobar emphysema

CLE results in overexpansion of a pulmonary lobe and resultant compression of the remaining lobes of the ipsilateral lung, and possibly also the contralateral lung. There is bronchial narrowing because of weakened or absent bronchial cartilage. There may be congenital extrinsic compression, commonly by an abnormally large pulmonary artery. This causes malformation of bronchial cartilage, making them soft and collapsible. CLE is potentially reversible, yet possibly life-threatening, causing respiratory distress in the neonate.

Paraseptal emphysema

Paraseptal emphysema is a type of emphysema which involves the alveolar ducts and sacs at the lung periphery. The emphysematous areas are subpleural in location and often surrounded by interlobular septa (hence the name). It may be an incidental finding in young adults, and may be associated with spontaneous pneumothorax. It may also be seen in older patients with centrilobular emphysema. Both centrilobular and paraseptal emphysema may progress to bullous emphysema. A bulla is defined as being at least 1cm in diameter, and with a wall less than 1mm thick. Bullae are thought to arise by air trapping in emphysematous spaces, causing local expansion.

Signs and symptoms

Emphysema is a disease of the lung tissue caused by destruction of structures feeding the alveoli, in some cases owing to the action of alpha 1-antitrypsin deficiency. This causes the small airways to collapse during forced exhalation, as alveolar collapsibility has decreased. As a result, airflow is impeded and air becomes trapped in the lungs, in the

same way as other obstructive lung diseases. Symptoms include shortness of breath on exertion, and an expanded chest. However, the constriction of air passages isn't always immediately deadly, and treatment is available. Most of the people who have emphysema are smokers. Damage caused by emphysema is permanent even after the person stops smoking. People with this disease do not get enough oxygen and cannot eradicate the carbon dioxide, so they always have a shortage of breath. Emphysema usually initially presents with dyspnea (shortness of breath) during physical activity. Eventually the person will notice that the dyspnea is occurring any time they are physically exerted. Finally, the person will be dyspneic all the time even when they are in a relaxed state. People with emphysema can have trouble coughing and lowered amounts of sputum. They can begin to lose weight and have tachypnea (rapid breathing) when they try to extend their expiration. Breathing is difficult and the patient must use accessory muscles to help them breathe. The patient can have an increase of the anteroposterior diameter of their chest which is sometimes referred as "barrel chest." The patient is often seen leaning forward with arms extended or leaning on something to help them breathe. When lung auscultation and chest percussion is done there is a hyperresonant sound that is heard. (Mc Cance) Emphysema patients can have symptoms of cyanosis, lowered oxygen levels and increased carbon dioxide levels.

Causes

The majority of all emphysema cases are caused by smoking tobacco. Emphysema cases that are caused by other etiologies are referred to as secondary emphysema.

In some cases it may be due to alpha 1-antitrypsin deficiency. Severe cases of A1AD may also develop cirrhosis of the liver, where the accumulated A1AT leads to a fibrotic reaction.

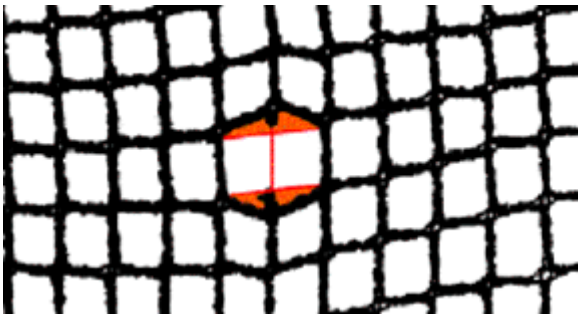
Some types of emphysema are considered a normal part of aging and are found in the elderly whose lungs have deteriorated due to age. At about 20 years of age, people stop developing new alveoli tissue. In the years following the cessation of the development of new alveoli, lung tissue can start to deteriorate. This is a normal, natural part of aging in healthy people. Alveoli will die, the number of lung capillaries will decline and the elastin of the lungs will begin to break down causing a loss of pulmonary elasticity. As people age, they will also lose strength and mass in their chest muscles causing these muscles to become weaker. In addition, bones can start to deteriorate and a person’s posture can change. Together, all of these age-related manifestations can cause the development of emphysema. Though not all elderly people will develop emphysema, they are all at risk of having decreased respiratory function.

Other causes of emphysema can be anything that causes the body to be unable to inhibit proteolytic enzymes in the lung. This could be exposure to air pollution, second hand smoke or other chemicals and toxins.

Pathophysiology

Pathology of lung showing centrilobular emphysema characteristic of smoking. Closeup of fixed, cut surface shows multiple cavities lined by heavy black carbon deposits. (CDC/Dr. Edwin P. Ewing, Jr., 1973)

In normal breathing, air is drawn in through the bronchi and into the alveoli, which are tiny sacs surrounded by capillaries. Alveoli absorb oxygen and then transfer it into the blood. When toxicants, such as cigarette smoke, are breathed into the lungs, the harmful particles become trapped in the alveoli, causing a localized inflammatory response. Chemicals released during the inflammatory response (e.g., elastase) can eventually cause the alveolar septum to disintegrate. This condition, known as septal rupture, leads to significant deformation of the lung architecture. The key mechanical event consequent to septal rupture is that the resulting cavity is larger than the sum of the two alveolar spaces (see side figure);



In red is the extra space of the new cavity after septal rupture due to the lung elastic recoil at the expenses of the surrounding healthy meshes (alveoli) Min Chir 1998,53:899-918.

in fact because of the lacking mechanical support of the broken septa the lung elastic recoil further enlarges this new space, necessarily at the expenses of the surrounding healthy parenchyma. In other words, as immediate and spontaneous consequence of septal rupture, the elastic lung recoil resets healthy parenchyma expansion at a lower level, in proportion to the amount of septal disruption.

The large cavities left by the septal rupture are known as **bullae (sin. = bulla)**. These deformations result in a large decrease of alveoli surface area used for gas exchange, as well as decreased ventilation of the surrounding healthy parenchyma. This results in a decreased Transfer Factor of the Lung for Carbon Monoxide (TLCO). To accommodate the decreased surface area, thoracic cage expansion (barrel chest) and diaphragm contraction (flattening) take place. Expiration, which physiologically depends completely on lung elastic recoil, increasingly depends on the thoracic cage and abdominal muscle action, particularly in the end expiratory phase. Due to decreased ventilation, the ability to exude carbon dioxide is significantly impaired. In the more serious cases, oxygen uptake is also impaired. As the alveoli continue to break down, hyperventilation is unable to compensate for the progressively shrinking surface area, and the body is not able to maintain high enough oxygen levels in the blood. The body's last resort is vasoconstricting appropriate vessels. This leads to pulmonary hypertension, which places increased strain on the right side of the heart, the side responsible for pumping deoxygenated blood to the lungs. The heart muscle thickens in order to pump more blood. This condition is often accompanied by the appearance of jugular venous distension. Eventually, as the heart continues to fail, it becomes larger and blood backs up in the liver.

Patients with alpha 1-antitrypsin deficiency (A1AD) are more likely to suffer from emphysema. A1AT inhibits inflammatory enzymes (such as elastase) from destroying the alveolar tissue. Most A1AD patients do not develop clinically significant emphysema, but smoking and severely decreased A1AT levels (10-15%) can cause emphysema at a young age. The type of emphysema caused by A1AD is known as *panacinar* emphysema (involving the entire acinus) as opposed to *centrilobular* emphysema, which is caused by smoking. Panacinar emphysema typically affects the lower lungs, while centrilobular emphysema affects the upper lungs. A1AD causes about 2% of all emphysema. Smokers with A1AD are at the greatest risk for emphysema. Mild emphysema can often develop into a severe case over a short period of time (1–2 weeks).

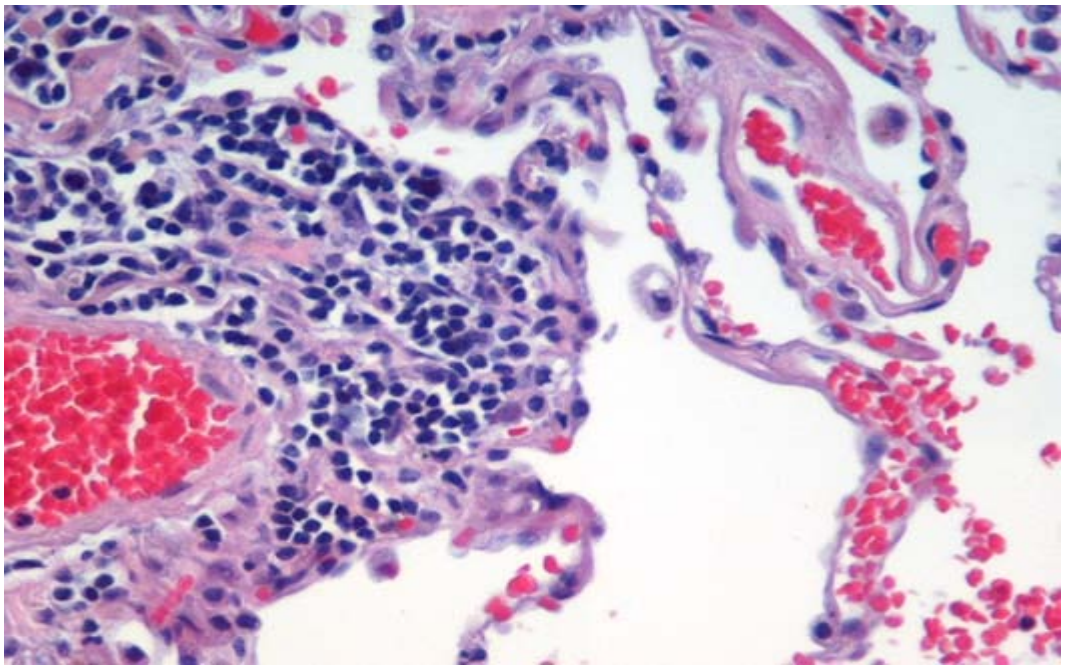
While A1AD provides some insight into the pathogenesis of the disease, hereditary A1AT deficiency only accounts for a small proportion of the disease. Studies for the better part of the past century have focused mainly upon the putative role of leukocyte elastase (also *neutrophil elastase*), a serine protease found in neutrophils, as a primary contributor to the connective tissue damage seen in the disease. This hypothesis, a result of the observation that neutrophil elastase is the primary substrate for A1AT, and A1AT is the primary inhibitor of neutrophil elastase, together have been known as the "*protease-antiprotease*" theory, implicating neutrophils as an important mediator of the disease. However, more recent studies have brought into light the possibility that one of the many other numerous proteases, especially matrix metalloproteases might be equally

or more relevant than neutrophil elastase in the development of non-hereditary emphysema.

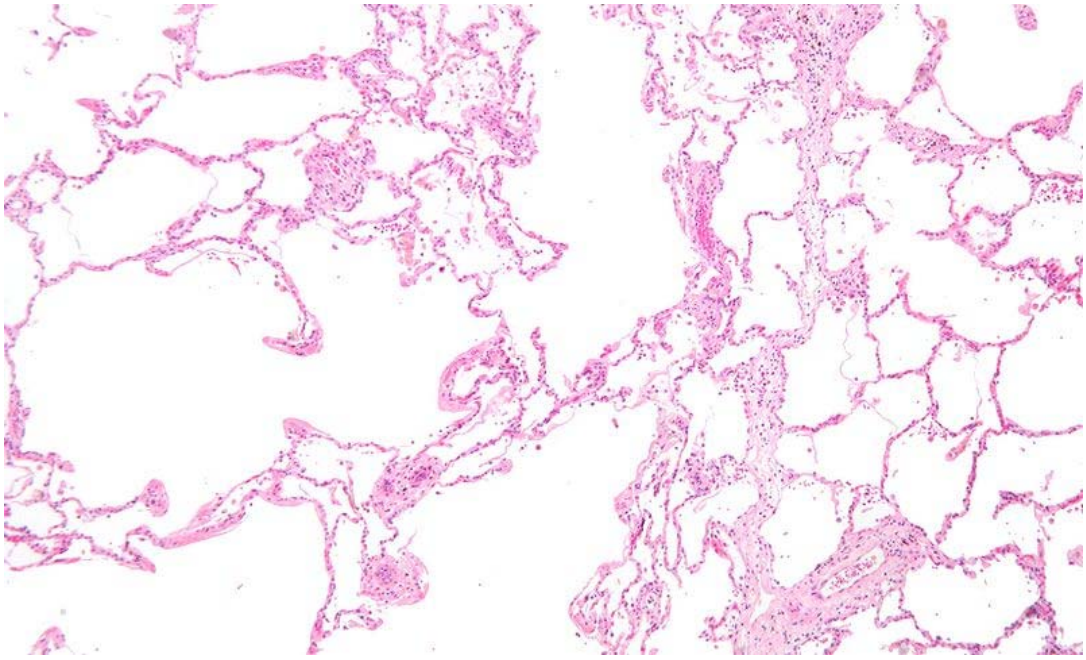
The better part of the past few decades of research into the pathogenesis of emphysema involved animal experiments where various proteases were instilled into the trachea of various species of animals. These animals developed connective tissue damage, which was taken as support for the protease-antiprotease theory. However, just because these substances can destroy connective tissue in the lung, as anyone would be able to predict, doesn't establish causality. More recent experiments have focused on more technologically advanced approaches, such as ones involving genetic manipulation. One particular development with respect to our understanding of the disease involves the production of protease "knock-out" animals, which are genetically deficient in one or more proteases, and the assessment of whether they would be less susceptible to the development of the disease. Often individuals who are unfortunate enough to contract this disease have a very short life expectancy, often 0–3 years at most.

Diagnosis

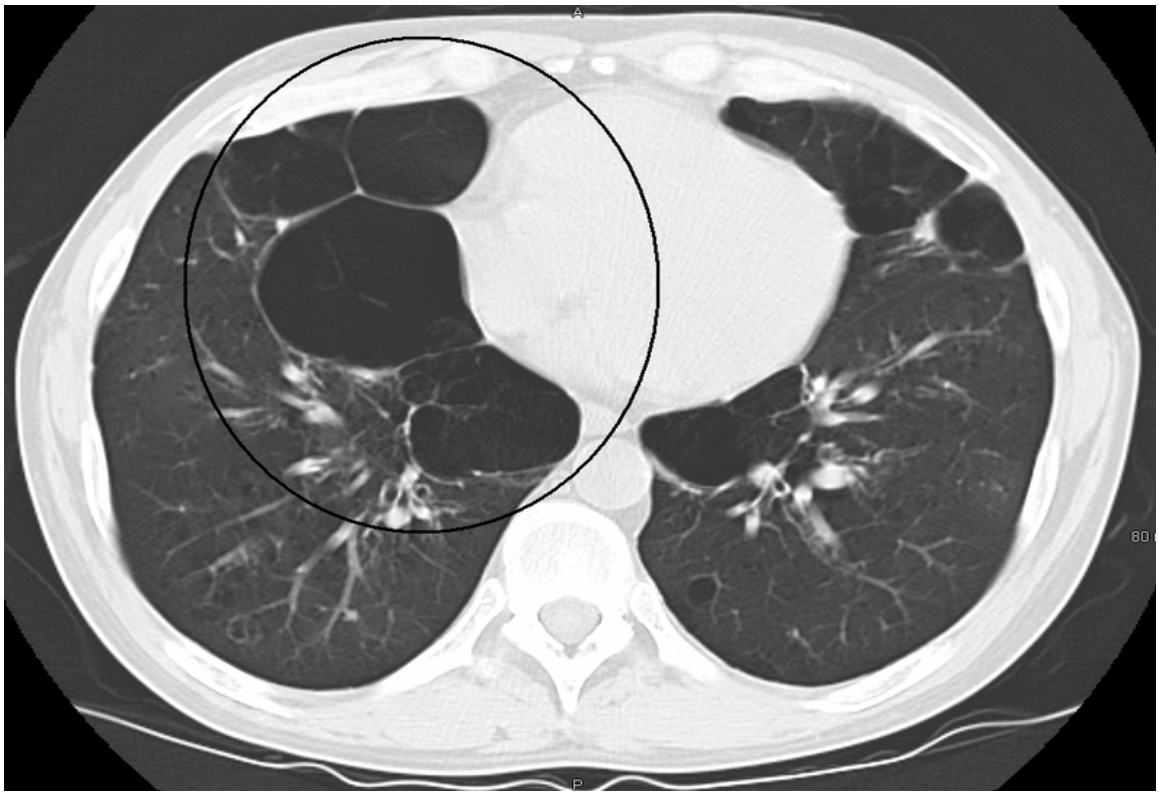
The diagnosis is usually confirmed by pulmonary function testing (e.g. spirometry); however, X-ray radiography may aid in the diagnosis. A DLCO test may be used to differentiate Emphysema from other types of Obstructive disorders such as Chronic Bronchitis and Asthma. DLCO is a test that measures the ability of gases to diffuse across the alveolar-capillary membrane. A DLCO will be decreased in Emphysema whereas it will be normal or increased in Asthma and Chronic Bronchitis.



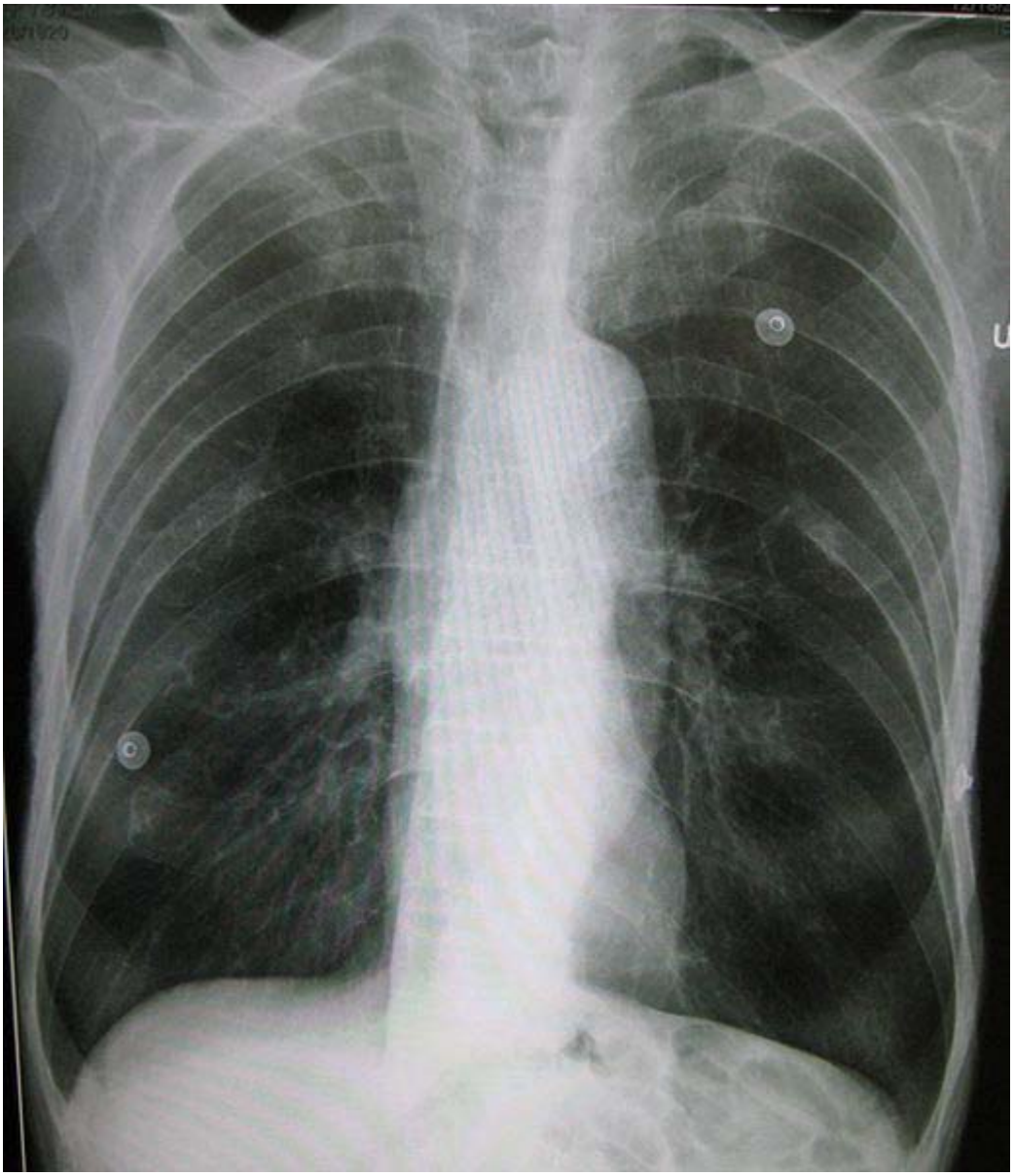
H&E stained lung tissue of end-stage emphysema. RBCs are red, nuclei are purple, other material is pink, and air spaces are white.



Micrograph demonstrating emphysema (left of image - large empty spaces) and lung tissue with relative preservation of the alveoli (right of image). H&E stain.



Axial CT image of the lung of a person with end-stage bullus emphysema



A severe case of emphysema

Management

Emphysema is also treated by supporting the breathing with anticholinergics, bronchodilators, steroid medication (inhaled or oral), effective body positioning (High Fowlers), and supplemental oxygen as required. Treating the patient's other conditions including gastric reflux and allergies may improve lung function. Supplemental oxygen used as prescribed (usually more than 20 hours per day) is the only non-surgical treatment which has been shown to prolong life in emphysema patients. There are lightweight portable oxygen systems which allow patients increased mobility. Patients can fly, cruise, and work while using supplemental oxygen. Other medications are being researched.

Lung volume reduction surgery (LVRS) can improve the quality of life for certain carefully selected patients. It can be done by different methods, some of which are minimally invasive. In July 2006 a new treatment, placing tiny valves in passages leading to diseased lung areas, was announced to have good results, but 7% of patients suffered partial lung collapse. The only known "cure" for emphysema is lung transplant, but few patients are strong enough physically to survive the surgery. The combination of a patient's age, oxygen deprivation and the side-effects of the medications used to treat emphysema cause damage to the kidneys, heart and other organs. Surgical transplantation also requires the patient to take an anti-rejection drug regimen which suppresses the immune system, and can lead to microbial infection of the patient. Patients who think they may have contracted the disease are recommended to seek medical attention as soon as possible.

Emphysema is an irreversible degenerative condition. The most important measure to slow its progression is for the patient to stop smoking and avoid all exposure to cigarette smoke and lung irritants. Pulmonary rehabilitation can be very helpful to optimize the patient's quality of life and teach the patient how to actively manage his or her care.

Notable cases

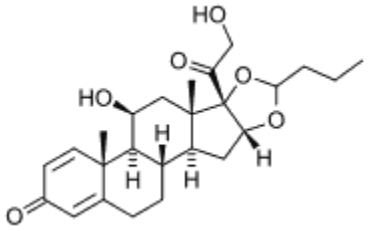
- Spencer Tracy
- R. J. Reynolds, R. J. Reynolds Jr., R. J. Reynolds, III,
- Don Imus
- Leonard Nimoy
- Paul Avery

Chapter 15

Budesonide and Inhaler

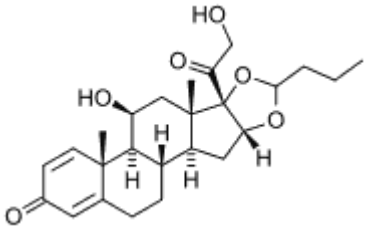
Budesonide

Budesonide



Systematic (IUPAC) name	
16,17-(butylidenebis(oxy))-11,21-dihydroxy-, (11-β,16-α)-pregna-1,4-diene-3,20-dione	
Identifiers	
CAS number	51333-22-3
ATC code	A07EA06 D07AC09, R01AD05, R03BA02
PubChem	CID 40000
DrugBank	APRD00442
ChemSpider	36566 ✓
ChEMBL	CHEMBL1370 ✓
Chemical data	
Formula	$C_{25}H_{34}O_6$
Mol. mass	430.534 g/mol
SMILES	eMolecules & PubChem
Pharmacokinetic data	

Bioavailability	10-20% (first pass effect)
Protein binding	85-90%
Metabolism	Hepatic CYP3A4
Half-life	2.0-3.6 hours
Excretion	Renal, Faecal
Therapeutic considerations	
Pregnancy cat.	C(US)
Legal status	POM (UK) ℞-only (US)
Routes	Oral, Nasal, tracheal, rectal



Budesonide is a glucocorticoid steroid for the treatment of asthma, non-infectious rhinitis (including hay fever and other allergies), and for treatment and prevention of nasal polyposis. Additionally, it is used for Crohn's disease (inflammatory bowel disease).

It is marketed by AstraZeneca as a nasal inhalant under the brand name **Rhinocort** (in Denmark, as **Rhinosol**), as an oral inhalant under the brand name **Pulmicort** (in Israel, **Budicort**), and as either an enema or a modified release oral capsule under the brand name **Entocort**. It is also sold in combination with formoterol (Oxis) in a single inhaler, under the brand name **Symbicort**. In Brazil it's marketed by Eurofarma under the brand name **Noex**. **Entocort EC** is an oral capsule marketed in the United States by Prometheus Laboratories.

A new formulation is in clinical trials for ulcerative colitis.

Pharmacology

Budesonide has a high first-pass metabolism. It has efficacy in the terminal ileum and the right colon.

Budesonide in comparison with prednisolone has been associated with fewer bone density losses and unlike other corticosteroids has little influence on the hypothalamic-pituitary-adrenal axis, which also limits the need of tapering before discontinuation. Overall, it has a lower incidence of systemic manifestations than similar medications.

Side Effects

Budesonide may cause:

- nose irritation or burning
- bleeding or sores in the nose
- lightheadedness
- upset stomach
- cough
- hoarseness
- dry mouth
- rash
- sore throat
- bad taste in mouth
- change in mucus color

In addition the following symptoms should be reported immediately:

- difficulty breathing or swelling of the face
- white patches in the throat, mouth, or nose
- irregular menstrual periods
- severe acne
- rarely, behavioral changes—when these do occur, they seem to mostly affect children.

Recall

Pulmicort inhalers were recalled by AstraZeneca in 2004 because there was concern that they may not always have provided the full dosage.

Misuse or Abuse

In its Fiscal Year 2010 Work Plan, the Office of the Inspector General (OIG) of the United States Department of Health and Human Services, stated that it would be investigating whether the number of units of budesonide billed and paid for by Medicare in South Florida exceeds the amount of the drug actually distributed in the area. The OIG noted that its previous work had revealed "aberrant billing patterns" for inhaled budesonide in South Florida, and stated that it believes many of these billings may be fraudulent.

Inhaler

A metered-dose inhaler (MDI)

Disposable inhalers

An **inhaler** or **puffer** is a medical device used for delivering medication into the body via the lungs. It is mainly used in the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD). Zanamivir (Relenza), used to treat influenza, must be administered via inhaler. To reduce deposition in the mouth and throat, and to reduce the need for precise synchronization of the start of inhalation with actuation of the device, MDIs are sometimes used with a complementary spacer or holding chamber device.

Types

Metered-dose inhalers

The most common type of inhaler is the pressurized metered-dose inhaler (MDI). In MDIs, medication is most commonly stored in solution in a pressurized canister that contains a propellant, although it may also be a suspension. The MDI canister is attached to a plastic, hand-operated actuator. On activation, the metered-dose inhaler releases a fixed dose of medication in aerosol form. The correct procedure for using an MDI is to first fully exhale, place the mouth-piece of the device into the mouth, and having just started to inhale at a moderate rate, depress the canister to release the medicine. The aerosolized medication is drawn into the lungs by continuing to inhale deeply before holding the breath for 10 seconds to allow the aerosol to settle onto the walls of the bronchial and other airways of the lung.

Dry powder inhalers

Dry powder inhalers (DPI) release a dose of medicine as a powder aerosol.

Nebulizers

Nebulizers supply the medication as an aerosol created from an aqueous formulation.

Analgesic inhalers

In 1968, Robert Wexler of Abbott Laboratories developed the Analgizer, a disposable inhaler that allowed the self-administration of methoxyflurane vapor in air for analgesia. The Analgizer consisted of a polyethylene cylinder 5 inches in length and 1 inch in diameter with a 1 inch long mouthpiece. The device contained a rolled wick of polypropylene felt which held 15 milliliters of methoxyflurane. Because of the simplicity of the Analgizer and the pharmacological characteristics of methoxyflurane, it was easy for patients to self-administer the drug and rapidly achieve a level of conscious analgesia which could be maintained and adjusted as necessary over a period of time lasting from a few minutes to several hours. The 15 milliliter supply of methoxyflurane would typically last for two to three hours, during which time the user would often be partly amnesic to the sense of pain; the device could be refilled if necessary. The Analgizer was found to be safe, effective, and simple to administer in obstetric patients during childbirth, as well as for patients with bone fractures and joint dislocations, and for dressing changes on burn patients. When used for labor analgesia, the Analgizer allows labor to progress normally and with no apparent adverse effect on Apgar scores. All vital signs remain normal in obstetric patients, newborns, and injured patients. The Analgizer was widely utilized for analgesia and sedation until the early 1970s, in a manner that foreshadowed the patient-controlled analgesia infusion pumps of today. The Analgizer inhaler was withdrawn in 1974, but use of methoxyflurane as a sedative and analgesic continues in Australia and New Zealand in the form of the Penthrox inhaler.

Propellants

Recently, the FDA banned the use of inhalers that utilize CFCs (Chlorofluorocarbons) as propellants for the more the environmentally friendly HFA inhalers. While some asthma suffers and advocacy groups contend that these environmentally friendly inhalers are not as effective, published clinical studies indicate equivalent control of asthma is achieved with use of HFA inhalers. Patients also are concerned with the high price of the HFA inhalers as there is no generic version, which was available in the CFC inhalers for many years. Inhalers used to treat asthma contains dry powder spin inhalers and aerosoles containing suspending liquid medicament, but in both the cases the size of suspended particles or powder particles must be less than 5 micrometres so as to increase the surface area and deliver the drug to the inner most areas. Such a sufficiently small size of particles is necessary for dispersion and also for rapid action.