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Leprosy
Leprosy or Hansen's disease (HD) is a chronic disease caused by the bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*. Named after physician Gerhard Armauer Hansen, leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract; skin lesions are the primary external sign. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs and eyes. Contrary to folklore, leprosy does not cause body parts to fall off, although they can become numb or diseased as a result of secondary infections; these occur as a result of the body's defenses being compromised by the primary disease. Secondary infections, in turn, can result in tissue loss causing fingers and toes to become shortened and deformed, as cartilage is absorbed into the body.

Although the mode of transmission of Hansen's disease remains uncertain, most investigators think that *M. leprae* is usually spread from person to person in respiratory droplets. Studies have shown that leprosy can be transmitted to humans by armadillos. Leprosy is now known to be neither sexually transmitted nor highly infectious after treatment. Approximately 95% of people are naturally immune and sufferers are no longer infectious after as little as 2 weeks of treatment.

The minimum incubation period reported is as short as a few weeks, based on the very occasional occurrence of leprosy among young infants. The maximum incubation period reported is as long as 30 years, or over, as observed among war veterans known to have been exposed for short periods in endemic areas but otherwise living in non-endemic areas. It is generally agreed that the average incubation period is between three and five years.

Leprosy has affected humanity for over 4,000 years, and was well-recognized in the civilizations of ancient China, Egypt, and India. In 1995, the World Health Organization (WHO) estimated that between 2 and 3 million people were permanently disabled because of leprosy at that time. In the past 20 years, 15 million people worldwide have been cured of leprosy. Although the forced quarantine or segregation of patients is unnecessary in places where adequate treatments are available, many leper colonies still remain around the world in countries such as India (where there are still more than 1,000 leper colonies), China, Romania, Egypt, Nepal, Somalia, Liberia, Vietnam, and Japan. Leprosy was once believed to be highly contagious and was treated with mercury — all of which applied to syphilis, which was first described in 1530. It is now thought that many early cases of leprosy could have been syphilis.

The age-old social stigma associated with the advanced form of leprosy lingers in many areas, and remains a major obstacle to self-reporting and early treatment. Effective treatment for leprosy appeared in the late 1930s with the introduction of dapsone and its derivatives. Leprosy bacilli resistant to dapsone soon evolved and, due to overuse of dapsone, became widespread. It was not until the introduction of multidrug therapy (MDT) in the early 1980s that the disease could be diagnosed and treated successfully within the community.

MDT for multibacillary leprosy consists of rifampicin, dapsone, and clofazimine taken over 12 months. Dosages adjusted appropriately for children and adults are available in all primary health centres in the form of blister packages. Single dose MDT for single lesion leprosy consists of rifampicin, ofloxacin, and minocycline. The move toward single-dose treatment strategies has reduced the prevalence of disease in some regions, since prevalence is dependent on duration of treatment.
World Leprosy Day was created to draw awareness to leprosy and its sufferers.

There are several different approaches for classifying leprosy; however, parallels exist.

- The World Health Organization system distinguishes "paucibacillary" and "multibacillary" based upon the proliferation of bacteria ("pauci-" refers to a low quantity.)
- The SHAY scale provides five gradations.
- The ICD-10, though developed by the WHO, uses Ridley-Jopling and not the WHO system. It also adds an indeterminate ("I") entry.
- In MeSH, three groupings are used.

<table>
<thead>
<tr>
<th>WHO</th>
<th>Ridley-Jopling</th>
<th>ICD-10</th>
<th>MeSH</th>
<th>Description</th>
<th>Lepromin test</th>
<th>Immune target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paucibacillary</td>
<td>&quot;TT&quot;</td>
<td>A30.1, A30.2</td>
<td>Tuberculoid</td>
<td>It is characterized by one or more hypopigmented skin macules and anaesthetic patches, where skin sensations are lost because of damaged peripheral nerves that have been attacked by the human host's immune cells. Borderline leprosy is of intermediate severity and is the most common form. Skin lesions resemble tuberculoid leprosy but are more numerous and irregular; large patches may affect a whole limb, and peripheral nerve involvement with weakness and loss of sensation is common. This type is unstable and may become more like lepromatous leprosy or may undergo a reversal reaction, becoming more like the tuberculoid form.</td>
<td>Positive</td>
<td>bacillus (Th1)</td>
</tr>
<tr>
<td>Multibacillary or borderline</td>
<td>&quot;BB&quot;</td>
<td>A30.3</td>
<td>Borderline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Multibacillary lepromatous ("BL"), and lepromatous ("LL")

A30.4, A30.5 Lepromatous

It is associated with symmetric skin lesions, nodules, plaques, thickened dermis, and frequent involvement of the nasal mucosa resulting in nasal congestion and epistaxis (nose bleeds), but, typically, detectable nerve damage is late.

There is a difference in immune response to the tuberculoid and lepromatous forms.

Hansen's disease may also be divided into the following types: 344-346

- Early and indeterminate leprosy
- Tuberculoid leprosy
- Borderline tuberculoid leprosy
- Borderline leprosy
- Borderline lepromatous leprosy
- Lepromatous leprosy
- Histoid leprosy
- Diffuse leprosy of Lucio and Latapí

This disease may also occur with only neural involvement, without skin lesions. This disease is also known as Hansen's Disease.

Skin lesions are the primary external sign. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs, and eyes.

Diagnosis in the U.S. is often delayed because healthcare providers are unaware of leprosy and its symptoms. Early diagnosis and treatment prevents nerve involvement, the hallmark of leprosy, and the disability it causes.

There are many kinds of leprosy but there are common symptoms. These include runny nose, dry scalp, eye problems, skin lesions, and muscle weakness.
Mycobacterium leprae

*Mycobacterium leprae*, one of the causative agents of leprosy. As acid-fast bacteria, *M. leprae* appear red when a Ziehl-Neelsen stain is used.

Main article: Mycobacterium leprae

At highest risk are those living in endemic areas with poor conditions such as inadequate bedding, contaminated water, and insufficient diet, or other diseases that compromise immune function. However, though hard evidence is limited, and fringe publications have made passionate claims to the contrary, professional studies show little evidence that HIV is an important factor in increasing the risk of leprosy infection. It is presumed that this might be because of differences between the modes of immunity involved. However, it is plain that the two infections and their signs and progressions need not be fully independent, so the matter should be regarded with reserve. For example, a Medscape clinical presentation reports that HIV infection neither is a risk factor for acquisition nor for increased virulence of leprosy, but that latent cases of leprosy may emerge after starting HAART. Lewis, F. S. et al.; Dermatologic Manifestations of Leprosy Clinical Presentation

Recent research suggests that there is a defect in cell-mediated immunity that causes susceptibility to Hansen's disease. Less than ten percent of the world's population is capable of acquiring the disease. The region of DNA responsible for this variability is also involved in Parkinson disease, giving rise to current speculation that the two disorders may be linked in some way at the biochemical level. In early 2003, an international team of scientists conducted a genome scan in Vietnamese multiplex leprosy families and found that susceptibility to leprosy was significantly linked to region q25 on the long arm of chromosome 6. Further confirmation of the chromosome 6 locus was provided by high-resolution linkage mapping in simplex leprosy families. Now, in a continuation of these findings, the team has pinpointed the chromosome 6 susceptibility locus to the 5' regulatory promoter region shared by both the Parkinson's disease gene PARK2 and its co-regulated gene PACRG. According to The Leprosy Mission Canada, most people—about 95% of the population—are naturally immune to the disease.

The mechanism of transmission of leprosy is prolonged close contact and transmission by nasal droplet. In addition to humans, leprosy has been observed in nine-banded armadillo, (which, it has recently been confirmed, are among the primary sources of new cases of leprosy in Americans), and three species of primates. The bacterium can also be grown in the laboratory by injection into the footpads of mice. There is evidence that not all people who are infected with *M. leprae* develop leprosy, and genetic factors have long been thought to play a role, due to the
observation of clustering of leprosy around certain families, and the failure to understand why certain individuals develop lepromatous leprosy while others develop other types of leprosy. It is estimated that due to genetic factors, only 5% of the population is susceptible to leprosy. This is mostly because the body is naturally immune to the bacteria, and those persons that do become infected experience severe allergic reactions to the disease. However, the role of genetic factors is not entirely clear in determining this clinical expression. In addition, malnutrition and prolonged exposure to infected persons may play a role in development of the overt disease.

The most widely held belief is that the disease is transmitted by contact between infected persons and healthy persons. In general, closeness of contact is related to the dose of infection, which in turn is related to the occurrence of disease. Of the various situations that promote close contact, contact within the household is the only one that is easily identified, although the incidence among contacts and the relative risk for them appear to vary considerably in different studies. In incidence studies, infection rates for contacts of lepromatous leprosy have varied from 6.2 per 1000 per year in Cebu, Philippines to 53 per 1000 per year in part of Western India to 55.8 per 1000 per year in a part of Southern India.\(^1\)

Two exit routes of \(M. \text{leprae}\) from the human body often described are the skin and the nasal mucosa, although their relative importance is not clear. Lepromatous cases show large numbers of organisms deep in the dermis, but whether they reach the skin surface in sufficient numbers is doubtful. Although there are reports of acid-fast bacilli being found in the desquamating epithelium (sloughing of superficial layer of skin) of the skin, Weddell \textit{et al.} had reported in 1963 that they could not find any acid-fast bacilli in the epidermis, even after examining a very large number of specimens from patients and contacts. In a recent study, Job \textit{et al.} found fairly large numbers of \(M. \text{leprae}\) in the superficial keratin layer of the skin of lepromatous leprosy patients, suggesting that the organism could exit along with the sebaceous secretions.

The importance of the nasal mucosa was recognized as early as 1898 by Schäffer, in particular that of the ulcerated mucosa. The quantity of bacilli from nasal mucosal lesions in lepromatous leprosy was demonstrated by Shepard as large, with counts ranging from 10,000 to 10,000,000. Pedley reported that the majority of lepromatous patients showed leprosy bacilli in their nasal secretions as collected through blowing the nose. Davey and Rees indicated that nasal secretions from lepromatous patients could yield as much as 10 million viable organisms per day.

The entry route of \(M. \text{leprae}\) into the human body is also not definitively known: The skin and the upper respiratory tract are most likely. While older research dealt with the skin route, recent research has increasingly favored the respiratory route. Rees and McDougall succeeded in the experimental transmission of leprosy through aerosols containing \(M. \text{leprae}\) in immune-suppressed mice, suggesting a similar possibility in humans. Successful results have also been reported on experiments with nude mice when \(M. \text{leprae}\) were introduced into the nasal cavity by topical application. In summary, entry through the respiratory route appears the most probable route, although other routes, particularly broken skin, cannot be ruled out. The CDC notes the following assertion about the transmission of the disease: "Although the mode of transmission of Hansen's disease remains uncertain, most investigators think that \(M. \text{leprae}\) is usually spread from person to person in respiratory droplets."
In leprosy, both the reference points for measuring the incubation period and the times of infection and onset of disease are difficult to define, the former because of the lack of adequate immunological tools and the latter because of the disease's slow onset. Even so, several investigators have attempted to measure the incubation period for leprosy. The minimum incubation period reported is as short as a few weeks and this is based on the very occasional occurrence of leprosy among young infants. The maximum incubation period reported is as long as 30 years, or over, as observed among war veterans known to have been exposed for short periods in endemic areas but otherwise living in non-endemic areas. It is generally agreed that the average incubation period is between three and five years.

**Prevention**

Because leprosy can be cured with medicines, an early diagnosis will often reduce leprosy symptoms and complications. Therefore, while prevention of leprosy is not always possible, especially where leprosy is endemic, control should be possible.

An early diagnosis of help reducing the severeness and complications caused by the disease as leprosy can be cured with medicines. Although the prevention is often difficult especially in the places where it is endemic, control can be possible. People in immediate contact with leprosy patients should examine themselves for the infection. Annual examinations for at least five years should be conducted for such people following their very last contact with the leprosy patient.

In a recent trial, a single dose of rifampicin reduced the rate at which contacts acquired leprosy in the two years after contact by 57%; 265 treatments with rifampicin prevented one case of leprosy in this period. A non-randomized study found that rifampicin reduced the number of new cases of leprosy by 75% after three years.

**BCG** offers a variable amount of protection against leprosy as well as against tuberculosis.

Efforts to overcome persistent obstacles to the elimination of the disease include improving detection, educating patients and the population about its cause, and fighting social taboos about a disease that has caused its patients throughout history to be considered "unclean" or "cursed by God" as outcasts. Leprosy is not a hereditary disease. Where taboos are strong, patients may be forced to hide their condition (and avoid seeking treatment) to avoid discrimination. The lack of
awareness about Hansen's disease can lead people to believe (falsely) that the disease is highly contagious and incurable.

The ALERT hospital and research facility in Ethiopia provides training to medical personnel from around the world in the treatment of leprosy, as well as treating many local patients. Surgical techniques, such as for the restoration of control of movement of thumbs, have been developed.

In 1988, Jacinto Convit was nominated for the Nobel Prize in Medicine, for developing a vaccine to fight leprosy, by combining a tuberculosis (TB) vaccines with Mycobacterium Leprae.

MDT anti-leprosy drugs: standard regimens

Enough synthetic pharmaceuticals that are effective against leprosy have by now been identified, and support a flexible choice of treatments. The WHO Study Group's report on the Chemotherapy of Leprosy in 1993 recommended two types of standard MDT regimen be adopted. The first was a 24-month treatment for multibacillary (MB or lepromatous) cases using rifampicin, clofazimine, and dapsone. The second was a six-month treatment for paucibacillary (PB or tuberculoid) cases, using rifampicin and dapsone. At the First International Conference on the Elimination of Leprosy as a Public Health Problem, held in Hanoi the next year, the global strategy was endorsed and funds provided to WHO for the procurement and supply of MDT to all endemic countries.

The disease was known in Ancient Greece as elephantiasis (elephantiasis graecorum). At various times blood was considered to be a treatment either as a beverage or as a bath. That of virgins or children was considered to be especially potent. This practice seems to have originated with the Ancient Egyptians but was also known in China. This practice persisted until at least 1790, when the use of dog blood was mentioned in De Secretis Naturae. Paracelsus recommended the use of lamb's blood and even blood from dead bodies was used.

Snakes were also used, according to Pliny, Aretaeus of Cappadocia, and Theodorus. Gaucher recommended treatment with cobra venom. Boinet, in 1913, tried increasing doses of bee stings (up to 4000). Scorpions and frogs were used occasionally instead of snakes. The excreta of Anabas (the climbing fish) was also tried.
Alternative treatments included scarification with or without the addition of irritants including arsenic and hellebore. Castration was also practiced in the Middle Ages.

A common pre-modern treatment of leprosy was chaulmoogra oil.

The oil has long been used in India as an Ayurvedic medicine for the treatment of leprosy and various skin conditions. It has also been used in China and Burma, and was introduced to the West by Frederic John Mouat, a professor at Bengal Medical College. He tried the oil as an oral and topical agent in two cases of leprosy and reported significant improvements in an 1854 paper.

This paper caused some confusion. Mouat indicated that the oil was the product of a tree *Chaulmoogra odorata*, which had been described in 1815 by William Roxburgh, a surgeon and naturalist, while he was cataloging the plants in the East India Company’s botanical garden in Calcutta. This tree is also known as *Gynocardia odorata*. For the rest of the 19th century, this tree was thought to be the source of the oil. In 1901, Sir David Prain identified the true chaulmoogra seeds of the Calcutta bazaar and of the Paris and London apothecaries as coming from *Taraktogenos kurzii*, which is found in Burma and Northeast India. The oil mentioned in the Ayurvedic texts was from the tree *Hydnocarpus wightiana*, known as *Tuvakara* in Sanskrit and *chaulmugra* in Hindi and Persian.

The first parenteral administration was given by the Egyptian doctor Tortoulis Bey, personal physician to the Sultan Hussein Kamel of Egypt. He had been using subcutaneous injections of creosote for tuberculosis and in 1894 administered subcutaneous injection of chaulmoogra oil in a 36-year-old Egyptian Copt who had been unable to tolerate oral treatment. After 6 years and 584 injections, the patient was declared cured.

An early scientific analysis of the oil was carried out by Frederick B. Power in London in 1904. He and his colleagues isolated a new unsaturated fatty acid from the seeds, which they named 'chaulmoogric acid'. They also investigated two closely related species: *Hydnocarpus anthelmintica* and *Hydnocarpus wightiana*. From these two trees they isolated both chaulmoogric acid and a closely related compound, 'hydnocarpus acid'. They also investigated *Gynocardia odorata* and found that it produced neither of these acids. Later investigation showed that 'taraktogenos' (*Hydnocarpus kurzii*) also produced chaulmoogric acid.

Another difficulty with the use of this oil was administration. Taken orally it is extremely nauseating. Given by enema may cause peri-anal ulcers and fissures. Given by injection the drug caused fever and other local reactions. Despite these difficulties, a series of 170 patients were reported in 1916 by Ralph Hopkins, the attending physician at the Louisiana Leper Home in Carville, Louisiana. He divided the patients into two groups - 'incipient' and 'advanced'. In the advanced cases, 25% (at most) showed any improvement or arrest of their condition; in the incipient cases, 45% reported an improvement or stabilization of the disease (mortality rates were 4% and 8%, respectively). The remainder absconded from the Home apparently in improved condition.
Given the apparent usefulness of this agent, a search began for improved formulations. Victor Heiser the Chief Quarantine Officer and Director of Health for Manila and Elidoro Mercado the house physician at the San Lazaro Hospital for lepers in Manila decided to add camphor to a prescription of chaulmoogra and resorcin, which was typically given orally at the suggestion of Merck and Company in Germany to whom Heiser had written. They found that this new compound was readily absorbed without the nausea that had plagued the earlier preparations.

Heiser and Mercado in 1913 then administered the oil by injection to two patients who were cured of the disease. Since this treatment was administered in conjunction with other materials, the results were not clear. A further two patients were treated with the oil by injection without other treatments and again appeared to be cured of the disease. The following year, Heiser reported a further 12 patients but the results were mixed.

Less toxic injectable forms of this oil were then sought. Between 1920 and 1922, a series of papers were published describing the esters of these oils. These may have been based on the work of Alice Ball - the record is not clear on this point and Ms Ball died in 1916. Trials of these esters were carried out in 1921 and appeared to give useful results.

These attempts had been preceded by others. Merck of Darmstadt had produced a version of the sodium salts in 1891. They named this sodium gynocardate in the mistaken belief that the origin of the oil was Gynocardia odorata. Bayer in 1908 marketed a commercial version of the esters under the name 'Antileprol'.

To ensure a supply of this agent Joseph Rock, Professor of Systematic Botany at the College of Hawaii, traveled to Burma. The local villagers located a grove of trees in seed, which he used to establish a plantation in 2,980 trees on the island of Oahu, Hawaii between 1921 and 1922.

The oil remained a popular treatment despite the common side effects until the introduction of sulfones in the 1940s. Debate about its efficacy continued until it was discontinued.

Modern drug treatment

MDT patient packs and blisters
Epidemiology

Worldwide, two to three million people are estimated to be permanently disabled because of leprosy. India has the greatest number of cases, with Brazil second and Myanmar third.

In 1999, the world incidence of Hansen's disease was estimated to be 640,000. In 2000, 738,284 cases were identified. In 2000, the World Health Organization (WHO) listed 91 countries in which Hansen's disease is endemic. India, Burma, and Nepal contained 70% of cases. India reports over 50% of the world's leprosy cases. In 2002, 763,917 new cases were detected worldwide, and in that year the WHO listed Brazil, Madagascar, Mozambique, Tanzania, and Nepal as having 90% of Hansen's disease cases.

Although annual incidence — the number of new leprosy cases occurring each year — is important as a measure of transmission, it is difficult to measure in leprosy due to its long incubation period, delays in diagnosis after onset of the disease, and the lack of laboratory tools to detect leprosy in its very early stages. Instead, the registered prevalence is used. Registered prevalence is a useful proxy indicator of the disease burden, as it reflects the number of active leprosy cases diagnosed with the disease and receiving treatment with MDT at a given point in time. The prevalence rate is defined as the number of cases registered for MDT treatment among the population in which the cases have occurred, again at a given point in time.

New case detection is another indicator of the disease that is usually reported by countries on an annual basis. It includes cases diagnosed with onset of disease in the year in question (true incidence) and a large proportion of cases with onset in previous years (termed a backlog prevalence of undetected cases).

Endemic countries also report the number of new cases with established disabilities at the time of detection, as an indicator of the backlog prevalence. Determination of the time of onset of the disease is, in general, unreliable, is very labor-intensive, and is seldom done in recording these statistics.
G. H. A. Hansen, discoverer of *M. leprae*

DNA taken from the shrouded remains of a man discovered in a tomb next to the Old City of Jerusalem shows him to be the earliest human proven to have suffered from leprosy. The remains were dated by radiocarbon methods to 1-50 C.E.

After the end of the 17th century, Norway, Iceland and England were the countries in Western Europe where leprosy was a significant problem. During the 1830s, the number of lepers in Norway, Iceland and England rose rapidly, believed to be caused by frequent visits of sailors who visited Western India, causing an increase in medical research into the condition, and the disease became a political issue. Norway appointed a medical superintendent for leprosy in 1854 and established a national register for lepers in 1856, the first national patient register in the world. *Mycobacterium leprae*, the causative agent of leprosy, was discovered by G. H. Armauer Hansen in Norway in 1873, making it the first bacterium to be identified as causing disease in humans. The principal opposition to Hansen's view that leprosy was an infectious disease came from his father-in-law, Daniel Cornelius Daniellsen who considered it a hereditary disease and had stated this in his book, ‘‘Traité de la Spedalskhed ou Elephantiasis des Grecs’’ - the standard reference book on leprosy from 1848 until the death of Daniellsen in 1895.

Hansen observed a number of nonrefractile small rods in unstained tissue sections. The rods were not soluble in potassium lye, and they were acid- and alcohol-fast. In 1879, he was able to stain these organisms with Ziehl's method and the similarities with Koch's bacillus (*Mycobacterium tuberculosis*) were noted. There were three significant differences between these organisms: (1) the rods in the leprosy lesions were extremely numerous, (2) they formed characteristic intracellular collections (*globii*), and (3) the rods had a variety of shapes with branching and swelling. These differences suggested that leprosy was caused by an organism related to but distinct from *Mycobacterium tuberculosis*.

He worked at *St. Jørgens Hospital* in Bergen, founded early in the fifteenth century. St. Jørgens is today a museum, *Lepramuseet*, it can be argued the best-preserved leprosy hospital in Northern Europe.
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