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# A Review of Hansen's Disease

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BIOL370: Introduction to Microbiology

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Hansen's Disease, better known as Leprosy, is a bacterial disease afflicting 150 people in the United States and 250,000 worldwide each year (1). The disease is found mostly in warm and wet areas of the tropics, with eighty percent of all cases are found in India, Indonesia, Myanmar, Brazil and Nigeria (2). Most people (95% of the world population) have natural immunity to this disease; however, Hansen's Disease still poses a risk in regions with underdeveloped healthcare infrastructures. Transmission of the disease occurs primarily through long term contact with someone who is untreated for Hansen's Disease. The disease cannot be transmitted after short term physical contact, including from gestures like handshakes or eating together (4). The exact mode of transmission is still a mystery.

Though many infected persons may be asymptomatic, there are common symptoms associated with Hansen's Disease. The infecting pathogen, *Mycobacterium leprae* damages the skin, nerves, and nasal mucosa, so most symptoms manifest in these parts of the body. Patients may experience loss of sensation, numbness, development of skin nodules, redness of skin, and thickened, dry skin. In extreme cases where the facial nerves are affected, the patient may have eye problems that develop into blindness. For patients with extensive nerve damage, the loss of sensation can lead to the inability to detect injuries to the skin. People with Hansen's disease may develop open wounds as a result and left unrecognized, these wounds can lead to more serious secondary infections (5).

Research and treatment of Hansen's disease focuses on the causative agent, *M. leprae*. *M. leprae* is an aerobic, acid-fast bacillus. *M. leprae* is an obligately intracellular bacterial pathogen and thus studying this bacterium is difficult as it cannot be grown in a culture/grown in the lab. This characteristic of dependence on the host is supported by reductive evolution within *M. leprae*'s genome, a trait characteristic of obligate intracellular bacteria. With a genome size of 3.27 Mbp, genes required for transmission, small molecule synthesis (ex: amino acids, purines, pyrimidines), limited macromolecule synthesis (ex: ribosomes, RNA, some proteins), and metabolism of major metabolites are conserved. In contrast, genes involved in DNA repair, complex biosynthesis pathways, siderophore production, and oxidative respiratory chains have been largely lost (19-21). The reduction in genome size and increase in the fraction of pseudogenes is hypothesized to have been caused by *M. leprae*'s change from a free-living organism to host-dependent one (14).

Besides the inability to culture it in the lab, another characteristic of *M. leprae* that challenges physicians/researchers is that the pathogen replicates at a slow pace compared to other bacteria. This means hosts may be carrying the pathogen for years without realizing since the replication rate is so slow. The incubation period for the pathogen is approximately five years. Symptoms usually appear within one year, but can take up to twenty years, thus making early detection difficult (13). Since many classes of antibiotics target replicating cells, *M. leprae*'s slow rate of replication also permits resistance to many drugs (6).

Lastly, another mystery surrounding *M. leprae* is its mode of transmission. Researchers believe it is most likely transmitted through droplets spread from an infected person's coughs or sneezes (4). However, this hypothesis is still debated and actively being studied. Details on whether natural reservoirs contribute to its transmission and the exact different paths the pathogen can take within the body are also still being investigated (14).

Recent research does shed insight onto theories of how *M. leprae* causes peripheral neuropathy, however. The peripheral nerves are a major point of interest since the three general manifestations of Hansen's disease (Tuberculoid, Lepromatous, and Dimorphous Hansen's disease) all involve damage to the peripheral nerves (15). Scientists believe that the interaction between *M. leprae* and macrophages during infection is responsible for this damage. Once *M. leprae* invades the body's external defenses, it infects macrophages in the region. Macrophages can travel through the bloodstream to nerves, where they perform repair functions – this is one way researchers believe *M. leprae* can travel to nerve cells. When infected macrophages aggregate together, they form granulomas which are groups of immune cells that form when an infection occurs (9). The *M. leprae* within infected macrophages, has a specific lipid called phenolic glycolipid 1 (PGL-1) that triggers production of nitric oxide in macrophages. The increase in reactive nitrogen in a macrophage causes damage to nearby neuronal axons by damaging their mitochondria. Since many peripheral nerve cells are surrounded by a layers of insulating Schwann cells, the damage of mitochondria also leads to demyelination of neuronal axons (16). It is this damage to the nerve cells and axons caused by the innate immune response that causes the loss of sensation/perception of touch (6).

Fortunately, there are established diagnosis steps in place to detect an *M. leprae* infection. To prevent progression of Hansen's disease and minimize damage to nerve function, early diagnosis and prompt treatment are critical. Diagnosis includes looking for skin lesions, nodules, enlarged nerves, and sensory loss. Sensory loss is determined by prickling the afflicted area to see if the patient senses the stimuli. If the aforementioned symptoms are present, the leading physician can do skin or nerve biopsies and staining to get a positive identification of *M. leprae* (7). The Ziehl-Neelson method can also be used to do acid-fast staining for *M. leprae*; the detection of red-stained bacilli would mean a positive identification.

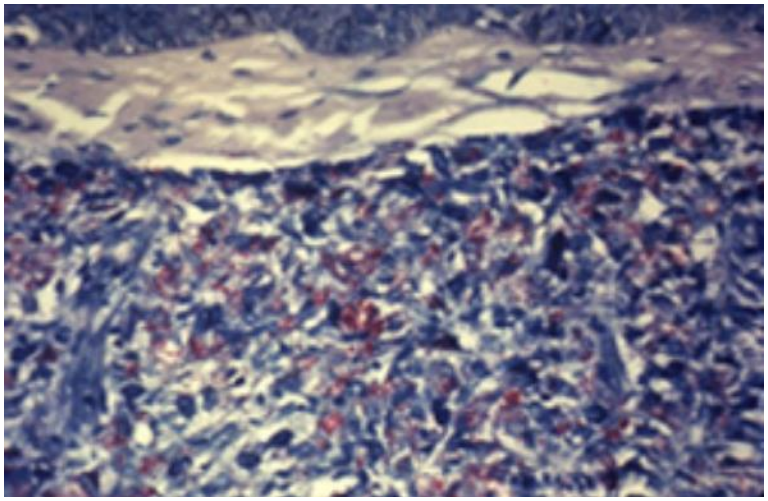

**Figure 1.** This photomicrograph shows an acid-fast stained tissue sample taken from a patient with leprosy. Red-stained *M. leprae* bacteria can be seen (8).

For determination of the type of Hansen's disease (Tuberculoid or Lepromatous for example), specific symptoms are used. For example, Paucibacillary (Tuberculoid) Hansen's disease is associated with a low count of bacteria on the skin/nerves (11) and characteristic hyperpigmented skin macules (15). On the other hand, Multibacillary (Lepromatous) Hansen's disease is associated with more bacteria present on skin/nerves (11) and "symmetrically-distributed skin lesions" (15). An additional lepromin skin test may be used to further differentiate the possible infections. A lepromin skin test involves inactivated *M. leprae* being injected underneath the skin and reviewing the injection site after three and twenty-eight days later to detect a reaction. A positive reaction indicates a type of tuberculoid leprosy, while a test detecting no reaction may indicate no infection or possible lepromatous leprosy (17) (more testing can be done in this case).

After a diagnosis has been made, physicians will use multi-drug therapy to treat the infection. Multi-drug therapy involves the use of two or more drugs to reduce the chances of antimicrobial resistance developing. For Hansen's disease, dapsone, rifampin, and/or clofazimine are used (10). However, the specific combination of drugs and treatment duration depends on the type of Hansen's disease. For Paucibacillary leprosy, adults are treated with rifampicin and dapsone for six months. For Multibacillary leprosy, adults are treated with rifampicin, dapsone, and clofazimine for twelve months (18). Some patients who experience allergic reactions to these drugs may be prescribed minocycline, ofloxacin, and clarithromycin as substitutes (11).

Even with antibiotic treatment, some patients in underdeveloped regions may experience secondary infections that cause permanent disability. For example, in severe cases, limbs can be lost due to the progression of secondary infections that pervaded the body when patients lost sensation from nerve damage. Treatment of secondary infections and surgery to aid in movement of limbs/injured body parts may improve quality of life for patients. Physicians will generally educate patients on the care of hands and feet as a preventative measure against permanent injury (11).

Multi-drug treatment is extremely effective and is recommended by the World Health Organization. Nonetheless, antimicrobial resistance and recurrence of Hansen's disease still occurs and poses threats to elimination of the disease. Cases have been identified of individuals with increased susceptibility to Hansen's disease, thus putting said individuals at increased chance of recurrence and reinfection. Genetic markers associated with leprosy in patients were analyzed in one study to identify "risk genes" and "particularly high susceptibility genetic profiles among leprosy patients predisposing to disease recurrence." The researchers identified risk alleles in genes such as the IL10 gene (anti-inflammatory cytokine), NOD2 gene (encodes a protein that is involved in recognition of bacterial LPS), and TLR1 gene (codes for toll-like receptors that recognize PAMPs on pathogens) (3, 22, 23). However, small sample sizes and limited genotyping limits the conclusions that can be drawn from this data; studies using widespread genomic analysis and larger sample sizes may provide more insight into recurrence and risk alleles.

Overall, the progress achieved in elucidating Hansen's Disease has been immense. Researchers have a general understanding of how M. leprae causes peripheral neuropathy, understand characteristic features of *M. leprae*, have the technology to perform genomic analyses on the pathogen, identified various types of the disease/how to approach each, multiple diagnosis steps are in place, and first-line drugs are highly effective in treating patients. New technology is also becoming more accessible and can aid in early detection. For example, qPCR and rapid quantitative serological tests for of *M. leprae* (NDO-LID and PGL1 tests) have recently been used for diagnosis. The latter in particular, are useful as such serological tests are a point-of-care method that can detect *M. leprae* before lesions first appear. They are also less costly than qPCR (which is highly accurate but expensive) and require no special equipment or extensive training to execute (24).

Despite the immense progress, research gaps still exist. Studies on the mode of transmission are ongoing as mentioned previously. Researchers are also combatting already evident cases of resistance to anti-leprosy drugs (to rifampin and dapsone in particular) as well as anticipating newer cases (12). Lastly, although newer technology such as NDO-LID/PGL1 serological tests and other molecular assays are available to improve the diagnosis process, these technologies have margins of error that have room for further improvement (error rates also differ depending on the type of Hansen's Disease).

Outside of scientific advances, changes to sociopolitical programs need to be implemented. The WHO's 2016-2020 Global Leprosy Strategy aimed for zero children diagnosed with leprosy and a rate of less than one per million diagnosed patients with visible deformities by 2020. The strategy included increased laboratory/program networking, community-based rehabilitation, contact management, and increased resources for leprosy patients (25). This initiative's goals have not been met however as endemic regions are still struggling to implement the WHO's suggestions without the necessary financial and healthcare infrastructure. A new global initiative/revamping of the previous strategy, efforts to improve available technology, and exploration of research gaps will steadily improve the outlook for Hansen's Disease worldwide.

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