Leprosy: a modern assessment of an ancient neglected disease
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ABSTRACT

Leprosy or Hansen’s disease is a chronic mycobacterial infectious disease caused by Mycobacterium leprae and affects mainly peripheral nerves and skin, as well as upper respiratory mucosae. This infection is a conjoined bacteriological and immunological disease. Target cells of infection are macrophages, histiocytes in the skin, and the nonmyelinating and myelinating Schwann cells in the peripheral nerves leading to axonal dysfunction and demyelination leading to functional impairment and deformity. Leprosy reactions represent the most important determinant of nerve impairment if untreated and unrecognized. Control of leprosy transmission remains a challenge despite substantial improvements through the use of multidrug therapy in many settings. Most importantly, although many patients have been microbiologically cured through the efforts of the World Health Organization, many are left with significant disability that has recently been estimated to be ~20% of those treated (~15 million individuals) in the last decades. Further efforts are needed to elucidate the epidemiology and risk factors for disability among those with multibacillary forms.

Key words: leprosy, bacteriological disease, immunological disease, multidrug therapy.

INTRODUCTION

Leprosy or Hansen’s disease (HD) is a chronic mycobacterial infectious disease caused by Mycobacterium leprae that affects mainly peripheral nerves and skin, as well as upper respiratory mucosae.¹ Far from nearing eradication, much remains to be done to control or ‘eliminate’ leprosy. This ancient disease continues to affect thousands of individuals worldwide, leaving many with permanent neurologic deficits.³

Leprosy is a conjoined bacteriological and immunological disease; this combined threat affects the clinical spectrum of the disease through variations in cellular immune response in susceptible hosts. Target cells of infection are macrophages, histiocytes in the skin, and the nonmyelinating and myelinating Schwann cells in the peripheral nerve leading to axonal dysfunction and demyelination.¹ Indeed, nerve injury plays a central role in the pathogenesis of leprosy, leading to functional impairment and deformity.³⁻⁵

Until now, there are persistent unresolved issues surrounding leprosy, most of which are as old as the disease itself. The precise mechanism of transmission of leprosy has not been conclusively defined.⁵ The mode of transmission of M. leprae is not well understood, but it is thought to be spread through respiratory inoculation followed by hematologic spread to skin and nerves as well as direct skin-to-skin contact from untreated borderline lepromatous (BL) and polar lepromatous (PL) cases.⁶ It is considered that >95% of individuals exposed to this bacterium are protected from developing infection and disease.

Worldwide, the prevalence of leprosy has decreased with the use of multidrug therapy (MDT). However, the global detection of new cases of leprosy remains a concern, indicating persistent infection transmission particularly in highly endemic settings.⁷⁻⁸ Interestingly, the nine-banded armadillo is the only immunologically intact animal that develops disseminated infections with M. leprae, and some sources claim that up to 50% of wild armadillos in Texas and Louisiana have naturally acquired leprosy.⁹⁻¹⁰ These infected armadillos represent a host reservoir along the Gulf Coast in the U.S., which may serve as a source

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of zoonotic infection for humans, and perhaps in other settings in the Americas.\textsuperscript{9}

**Global Epidemiology**

Leprosy is still a modernly relevant disease affecting millions of people worldwide. In 2004, 407,791 new cases of leprosy were reported to the World Health Organization (WHO) with a modest decrease to 296,499 in 2005.\textsuperscript{2-4} The highest incidences of these cases are in India, Brazil, Democratic Republic of Congo, Tanzania, Nepal, Mozambique, Madagascar, Angola, and Central African Republic, with 64\% of new cases worldwide occurring in India. Global leprosy trends vary widely among countries and within countries. In 2007, a total of 47,612 new cases were detected in 23 countries in Latin America, with Brazil, Colombia, and Paraguay the countries with the highest number of cases. A total of 64,715 prevalent cases were in treatment with MDT. Over the last two centuries, Mexico has contributed significantly to the fight against leprosy with prominent scientists such as Fernando Latapi, J. Castaneda, Amado Saul, and other internationally recognized leprologists to decrease the prevalence of cases, but the incidence to date remains stable.\textsuperscript{4} The contributions of these leprologists provided most of the bases for the public health and medical concepts to care for patients with leprosy in Mexico and elsewhere. Although the prevalence is far less, leprosy is still present in the U.S., with cases occurring among immigrant and endemic populations in Texas, Louisiana, Hawaii, Puerto Rico, and possibly California.\textsuperscript{9,10} Among the cases reported in the U.S. from 2005-2006, 75\% occurred in foreign-born patients.\textsuperscript{9}

By 2010, the effort led by the WHO contributed to have only four countries with a population of more than one million not reaching the goal of a prevalence level of less than one case per 10,000, with a total of 212,000 new identified cases globally. However, the goal of decreasing the rate of occurrence of new cases with disability (WHO Grade 2 disability) to a level below one case per million at the global level has not been reached.\textsuperscript{4}

**Microbiology**

\textit{M. leprae} bacillus is an obligate intracellular pathogen.\textsuperscript{11-14} No \textit{in vitro} culture methods have ever been successful, so laboratory research has been dependent on animal models such as the nine-banded armadillo, mouse foot pad models, and immunologically compromised knock-out mice. \textit{M. leprae} has many unique growth characteristics and requirements that differ from its better known relatives \textit{M. tuberculosis}, \textit{M. avis}, and \textit{M. bovis}. \textit{M. leprae} has an extremely long doubling time, which leads to an incubation period that averages 2-5 years but may be as long as 10 years. Also, \textit{M. leprae} survives better at cooler temperatures (approximately 27-33°C), which contributes to its preference for the skin and other cooler parts of the body such as nose, earlobes, and external aspect of upper and lower extremities.\textsuperscript{14}

Genetic sequencing has shed even more light on these differences, and it has been found that \textit{M. leprae}'s genome has undergone extensive reductive evolution compared to that of \textit{M. tuberculosis}.\textsuperscript{12,14} The overall genome of \textit{M. leprae} is smaller than \textit{M. tuberculosis} (3.3 Mb vs. 4.4 Mb), as well as having only less than half the number of open reading frames for potentially functional proteins as opposed to \textit{M. tuberculosis}.\textsuperscript{15} Also, \textit{M. leprae} has 1,133 pseudogenes vs. only six pseudogenes for \textit{M. tuberculosis}. This reduced genome has resulted in the loss of many metabolic pathways, decreased capacity for defense against toxic radicals, and deficient acquisition of iron from the environment, all contributing to \textit{M. leprae} status as an obligate intracellular organism.\textsuperscript{14}

**Immunopathogenesis**

Leprosy is an immunologically mediated disease with an intimate connection between the individual genetics of each host and the manifestations of the disease. Genetic influence in the development of leprosy is thought to be twofold. Genetics determines first an individual’s overall susceptibility or resistance to infection and, second, the degree of cellular immunity and delayed hypersensitivity mounted by each individual in response to the infection.\textsuperscript{1} Various loci of genetic susceptibility have been identified in specific cohorts including ubiquitination proteins, cellular messengers, and vitamin D receptors.\textsuperscript{14} As with many other diseases, human leukocyte antigen (HLA) associations have been linked to what type of leprosy develops in infected individuals. For example, HLA-DR3 has been associated with tuberculoid leprosy, whereas lepromatous disease develops more frequently in the subtypes HLA-DQ1 or HLA-MT1.\textsuperscript{12,14} In addition to HLA associations, the polar forms of the disease have different immunological pathways and cytokines that are responsible for their phenotypic characteristics. The tuberculoid pole (TT) is
governed by a predominantly Th1 immunological response in which cytokines such as IFNγ, IL-2, and lymphotoxin α cause an increase in phagocytic activity, leading to release of TNF and granuloma formation. In lepromatous leprosy (LL), however, there is a Th2 cellular response in which IL-4, IL-5, and IL-10 have been linked to an increased CD8 T-cell response that results in poor granuloma formation with a predominance of skin lesions. As is the case with the physical characteristics, borderline disease demonstrates dynamic movement between these poles.

Given the dependence of response to M. leprae infection on the cell-mediated immune system, particularly T-cells, there have been many inquiries about the possible interactions between leprosy and HIV. This is still an active area of research, but thus far it seems that M. leprae has a far less synergistic interaction with HIV than its relative M. tuberculosis. HIV does not appear to increase susceptibility to leprosy nor does it alter the clinical features of the disease or its response to therapy.14 Also, unlike M. tuberculosis, M. leprae does not accelerate the decline in immune function in HIV patients. Latent leprosy infection may be unmasked, however, as immune reconstitution disease after introduction of antiretrovirals and is often associated with type 1 reactions during MDT.11,14 With respect to other immunodeficient states besides HIV, there have been case reports of rapid development of LL in some patients receiving TNF monoclonal antibody therapy for arthritis as well as some patients receiving immunosuppressive therapy for transplantation.11

Clinical Spectrum
There are two classification schemes that characterize the type of leprosy (Table 1). The Ridley-Jopling staging system describes a continuum between tuberculoid (TT), borderline tuberculoid (BT), borderline borderline (BB), borderline lepromatous (BL), and LL (LL) based on clinical examination of the lesions, histopathological features, and bacillary index.13 However, because the Ridley-Jopling Spectrum is dependent on pathological data and expert opinion that may be impractical in the field, the WHO created a simplified classification system based solely on the number of skin lesions present. According to the WHO system, five or less lesions are classified as paucibacillary (PB) and six or more lesions is multibacillary (MB).2,4

| WHO and Ridley-Joplin classification of reactions across categories |
|--------------------------|----------------|----------------|----------------|----------------|
| Reaction type | PB* | Multibacillary (MB) |
| TT** | BT | BB | BL | LL |
| Type 1 | ----- | Type 1 | ----- | Type 2 |
| ----- | ----- | Type 2 | ----- |

*WHO, World Health Organization (Reference 2).
**Ridley-Joplin (Reference 13).

Leprosy is primarily a disease of the skin and nerves, and common presentations include appearance of skin lesions, numbness or weakness from nerve damage, or a burn or ulcer in a denervated area.1 Whereas the presentation is widely variable, the polar forms of the disease have characteristic features as a result of their type of interaction with the host immune system.

The TT pole of the disease is characterized by relatively effective cell-mediated immunity resulting in a few distinct macules or plaques.12 The lesions tend to be dry, scaly, hairless, and anesthetic due to the destruction of dermal nerve fibers.14 The color of the lesions depends on the patients’ skin tone and tends to be characteristically hypopigmented in darker skin tones or may appear copper colored in lighter skin.11 Histologically, biopsies show well-demarcated granulomas and rare AFB (acid-fast bacilli).1,12 The granulomatous infiltration of peripheral nerves causes palpable enlargement as well as sensory and motor loss in the nerve distribution. Nerve enlargement can also cause entrapment within fibro-osseous tunnels, which can occur separately or be exacerbated by immune reactions. Tuberculous disease generally carries a good prognosis with common self-healing and limited damage to peripheral nerves.11

The LL pole, on the other hand, is a disease state where patients have little to no resistance to the bacteria and demonstrate a highly infected state.13 LL is characterized by widely distributed, mildly hypopigmented and poorly defined papules and nodules.12 Biopsies of these lesions show sheets of foamy macrophages and large numbers of AFB.12,14 The high degree of dermal invasion in LL has significant physical and physiological implications. The characteristic “leonine facies” of leprosy is caused
by facial skin thickening and hair loss (madarosis), particularly of the eyelashes and eyebrows. Infiltration of the nasal mucosa is responsible for epistaxis and saddle deformity from septal perforation and destruction of the anterior nasal spine. Also, bacillary invasion of the testes is responsible for both atrophy and orchitis associated with type II immune reactions. Furthermore, destruction of dermal nerves causes a glove and stocking neuropathy with peripheral involvement developing later in the disease course.

Borderline leprosy is a continuous and unstable continuum of disease with features resembling both poles. Variability is wide, and the disease state is labeled as either borderline-tuberculoid (BT), borderline-borderline (BB), or borderline-lepromatous (BL), depending on which side of the spectrum it most reflects. The morphology of this state may be macular, papulo-nodular, plaques, annular, or geographic. There is also a small subset of patients with a form of non-nodular lepromatous disease, called Lucio HD, found mainly in areas of Mexico and Central America. Patients with this type of leprosy are predisposed for an extreme reaction called the Lucio phenomenon in which a severe vasculitis develops into thrombosis of blood vessels in the skin leading to hemorrhage, infarctions, and diffuse ulceration. The lesions are described as symmetrical, necrotic, stellate lesions on the extremities and face with hemorrhagic infarctions. This is a very extreme condition for which the only effective treatment is a long course of high-dose steroids and supportive care similar to that of burn patients.

Although commonly known for its skin manifestations, infection of peripheral nerves is the pathological hallmark of leprosy. Nerve involvement affects sensory nerves earliest and most commonly, but it also affects the motor and autonomic function of peripheral nerves. The most commonly affected nerves are the posterior tibial, ulnar, median, lateral popliteal, facial, greater auricular, radial, and radial cutaneous nerves. The progression of neurological deficits is related to the type of leprosy, as patients with fewer bacilli (TT and BT) generally present earlier with sensory and motor neuropathy, whereas LL patients develop neuropathy more slowly despite the fact that their nerves are more heavily infected. Interestingly, BL patients are reported to have the most extensive involvement of large nerves. Although for most types of the disease, skin lesions overlying a nerve trunk are associated with a significantly increased risk of nerve impairment, there is a form of leprosy called pure neuritic leprosy (PNL) that affects nerve trunks without any cutaneous signs. Furthermore, patients may experience silent neuropathy in which there is deterioration in sensory or motor function without any signs or symptoms of inflammation. Contributing factors to this silent neuropathy are thought to be cell-mediated inflammation, Schwann cell dysfunction, and post-inflammatory fibrosis.

The development of sensory and motor neuropathy contributes significantly to the morbidity of leprosy by putting patients at increased risk for disability and deformity. There are three main factors responsible for this increased risk. First, the impaired sensation predisposes patients to trauma and infections leading to tissue damage. Second, there is direct disability from decreased motor function, which may impair walking or handling of objects. Thirdly, destruction of dermal nerves leads to increased skin dryness and makes skin more vulnerable to surface damage. The effect of these principles is particularly damaging with respect to the eye. Blindness is estimated to affect ~3.2% of leprosy patients, which is especially devastating for those with concomitant loss of sensation. Eye damage may occur from either nerve damage or bacillary invasion of the skin or eye itself. The four main causes of vision loss include lagophthalmos, corneal ulceration, acute or chronic iridocyclitis, and secondary cataract. Lagophthalmos, the inability to close the eye properly, results from damage to the facial nerve due either to the disease itself or to immune reaction. Similarly, corneal ulceration largely results from damage to the ophthalmic branch of the trigeminal nerve. Also, involvement of the nasal mucosa may predispose to chronic infections of the lacrimal system.

The gold standard diagnosis is a full-thickness skin biopsy sample from an advancing margin of an active lesion, fixed in neutral-buffered formalin, embedded in paraffin, and examined by an experienced pathologist. The characteristics of interest are histological patterns such as granulomas, foamy macrophages in the dermis, involvement of cutaneous nerves, and specifically the identification of AFB within the nerves using a specialized Fite-Faraco modification of carboyl fuchsin stain. Due to many limiting factors of the above specifications, many facilities rely on a clinical diagnosis using the presence of skin lesions...
with definite sensory loss or thickened peripheral nerves or demonstration of *M. leprae* on slit-skin smears or histology of tissue as diagnostic criteria.\(^1\,12\) In recent years, PCR has been an “invaluable addition” to laboratory diagnosis and study of *M. leprae* but remains too costly for routine use. PCR-based tests have a specificity of 100% and sensitivity ranging from 34-80% for PB disease and 80-90%+ for MB disease. Also, PCR-based mutation detection analyses provide rapid drug susceptibility testing.\(^12\,14\) Due to the high sensitivity, however, results may be complicated by the fact that the PCR may detect DNA from dead bacilli, thus the signal may persist after treatment.\(^11\)

**Leprosy Reactions**

In addition to the wide spectrum of disease caused by *M. leprae* infection, the management of leprosy is further complicated by the development of immune reactions (types I and II), which may occur at any time before, during, or after treatment.\(^18\,19\) These reactions are associated with neuritis and painful skin lesions, which may be a significant source of morbidity separate from the consequences of bacterial replication. Reactions are classified as type I (reversal reaction) or type II (erythema nodosum lepromatum), which have different mechanisms, risk factors, and treatments.

Patients with polar tuberculoid HD (TT) are considered to have a stable form and do not have reactions. For the other subtypes, reactions may be classified as acute or chronic and mild or severe. Mild reactions are associated with only skin changes and no nerve involvement (i.e., neuritis, sensory or motor loss) and require only analgesic therapy. Severe reactions include any symptoms of nerve involvement, swelling of the face or extremities, or skin ulcerations. Severe reactions must be treated with a long course of high-dose steroids.\(^2\)

Neuritis is associated with both type I and II reactions and may result in permanent disability, thus the first priority in management of a reaction is to control the neuritis. Edema of extremities may be a presenting symptom of either type of reaction and should be addressed urgently.\(^1\,2\) Painful edema of the hands for more than a few days may result in stiffness and deformity of the fingers and permanent disability.\(^6\) In severe cases, splinting of the hands in a functional position during the acute phase may be helpful, followed by gradual mobilization to prevent functional loss.\(^2\)

Type I reactions, also called reversal reactions, occur among the borderline subtypes.\(^11\) The symptoms include inflammation and edema of skin lesions as well as neuritis.\(^6\) These reactions can occur at any time, but frequently occur shortly after beginning MDT.\(^16\,17\) The reactions represent an acute increase in immune function, which leads to an inflammatory response in affected areas.\(^6\) Histologically, biopsies from active reactions show edema, increased vascularity, and lymphocytic infiltration, all of which cause swelling and compression of nerves, eventually leading to fibrosis.\(^20\) Whereas this upgraded immune response may be good for bacillary clearance, the resulting neuritis and edema may cause permanent disability if not treated.\(^11\) Treatment of the reaction includes controlling the acute inflammation to ease pain and reverse eye and nerve pain. This is primarily achieved through high-dose oral corticosteroids followed by a slow taper. Additionally, clofazimine has been shown to have a steroid-sparing effect and the use of other immunosuppressant drugs.\(^12\)

Type II reactions are also known as erythema nodosum lepromatum (ENL) and occur in patients of either BL or LL subtype.\(^11\,18\,21\,24\) These reactions are systemic, affecting many organ systems. The onset is acute, but symptoms may become chronic or recurrent.\(^14\) Symptoms of ENL are diverse but most commonly include fever and painful red nodules or papules that commonly occur on the face and extensor surfaces.\(^6\) Deep lesions may progress to panniculitis, whereas a less common subtype of bullous ENL may actually ulcerate. Subcutaneous involvement may lead to tethering and fixation of joints. The common organ system effects include uveitis, neuritis, arthritis, dactylitis, lymphadenitis, orchitis, and nephritis. The proposed mechanism of action of these reactions is formation of antigen-antibody immune complexes combined with complement that are deposited in skin, blood vessel walls, nerves, and other organs leading to acute inflammation.\(^22\)

However, these immune complexes have not been identified in biopsies of the ENL lesions themselves.\(^6\) Studies during acute reactions have shown increases in circulating TNF in some individuals\(^19\,18\) as well as IFN\(\gamma\) and IL-12.\(^6\) Histological specimens show infiltration of neutrophils, edema, fragmented bacilli, and necrotizing vasculitis of blood vessels in the deep dermis and subcutaneous tissue.\(^6\)

The cornerstone of treatment of type II reactions is immunosuppression with high-dose corticosteroids.\(^11\) Additionally, thalidomide has a dramatic effect of initial
treatment and maintenance of reactions but is limited by teratogenicity and possible neurotoxicity. Recent studies reported conflicting results concerning the immunomodulatory effects of thalidomide thought to be responsible for its efficacy. Most suggest modulation of TNFα, IL-12, and IL-2 in stimulation of T-cell responses. Although clofazimine has a well-documented role in treatment of type I reactions, it is less effective than steroids and thalidomide for type II reactions. Additionally, it can take 4-6 weeks for the clofazimine to be effective, and its use may be limited by side effects of abdominal pain and diarrhea. However, there is no contraindication to using combinations of steroids, thalidomide, and clofazimine if all are required to gain control of a severe reaction.

**Treatment**

Clinical management of leprosy has been based on MDT since 1982 after resistance to dapson-only and dapsone-rifampin therapies was noticed. The first-line MDT combination recommended is a combination of rifampin, clofazimine, and dapsone. Although these drugs have great success in treating the infection, they carry a wide range of side effects ranging from inconvenient to potentially life-threatening. Rifampin is well known for its side effect of orange discoloration of body secretions. Clofazimine has many side effects including red-brown skin discoloration, conjunctival discoloration, darkening of involved skin areas, and ichthyosis of skin and forearms. Dapsone carries the risk of more serious complications including hemolysis in patients with G6PD deficiency, hypersensitivity syndrome, and even agranulocytosis. Second-line therapies include minocycline, and ofloxacin or pefloxacin. Notably, minocycline is also known to cause skin discoloration, usually of a grayish tone.

For MB disease, the WHO has reduced the treatment period from 24 to 12 months with all three first-line agents. However, some authors are still recommending the full 24-month course for patients with a bacillary index greater than four. Currently, the WHO recommendation for paucibacillary disease is divided into PB with a single lesion vs. PB with more than one lesion. For patients with more than one lesion, treatment is recommended for 6 months with dapsone and rifampin. For single-lesion disease, however, the recommendation is a single dose of “ROM therapy” (consisting of rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg). This recommendation is based on recent clinical trials from the WHO Technical Advisory Group on Leprosy Control comparing treatment of PB patients with single-dose ROM therapy vs. the conventional 6 month PB-MDT regimen. In these studies, single-lesion PB disease treated with the ROM therapy showed 88% clearance of lesions, whereas patients with 2-5 lesion disease experienced more than two times higher relapse rate in the ROM group vs. standard MDT group.

**Control or Elimination of Leprosy**

Leprosy has had a long and storied history in human populations, and treatment has certainly progressed from the days of the leprosarium. The development of MDT in 1982 as well as improved nutrition and living conditions in some areas saw large decreases in worldwide incidence, and some began to look toward eventual eradication of the disease. In 1991, the WHO established the goal of elimination (defined as prevalence of ≤1 case per 10,000 population) of leprosy by the year 2000, which was then pushed back to 2005. Since its inception, the program has treated more than 15 million people. By 2005, elimination had been achieved in 112 of the 122 endemic countries, and the WHO declared the “global target of leprosy elimination” to have been reached and decided to shift focus to the national level for the remaining countries. Although these numbers seem to herald vast advances in disease control, outspoken critics of the WHO’s focus on “elimination” over eradication feel that the strategy has been misguided and may end up underestimating the number of cases that still remain. These critics suggest the development of “post-elimination strategies” to address the needs of further case-control, detection, and treatment efforts in areas where elimination—but not eradication—has been reached.

In addition to further surveillance and continued commitment to MDT regimes, current research is still focused on trying to find a vaccine for the disease. Several possible vaccines have been considered for prevention of leprosy including BCG. Widespread BCG vaccination in Africa was shown to be effective against leprosy, whereas revaccination of school-aged children in the Brazilian Amazon region did not confer additional protection. Research continues, but a 2006 meta-analysis of experimental studies of BCG showed an average protection of 26%, with significant findings contributed to more than one dose having been administered as well as greater protection against development of multibacillary disease.
In summary, from ancient biblical allusions of social outcasts to current biopsychosocial difficulties of identification and treatment, leprosy is an age-old disease that has continued to be as medically challenging as it is culturally polarizing. Leprosy has an impressively wide spectrum of disease including both skin and nerve involvement resulting from the infection as well as the immune reactions that complicate the disease course and treatment. Antimicrobial MDT regimens and immunosuppressive therapies have been successful in the prevention of morbidity and mortality from the disease, although patients are still faced with long courses of treatment with numerous side effects. With hundreds of thousands of new cases reported each year, it is hoped that elimination efforts will continue to reduce the worldwide burden of disease as researchers continue to seek an effective vaccine. New resolutions passed by WHO target the unmet goals to achieve elimination of leprosy transmission and rehabilitation services with those with disabilities caused by leprosy infection.

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