

Treatment Gets Better, but Leprosy Remains a Global Problem[†]

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Rising standards of living and the provision of effective medical treatment have resulted in good control of leprosy in many parts of the world, but WHO-led efforts for the global elimination of leprosy by 2000 did not succeed. In several countries, however, ambitious and ill-advised attempts to meet the elimination goals led to changes in policies and case-reporting methods, prompting premature claims of victory.¹ Sometimes specialised clinics and services were dismantled, even in regions that still have many new patients.² One unintended consequence is that the number of patients now reported from many of these countries is unreliable and unrealistic, and probably the most accurate statement that can be made today is that, for the first time since the late 1970s, no accurate estimate is available for the number of cases of leprosy in the world.

Good medical treatment for *Mycobacterium leprae* infection is now widely available. Dapsone, the initial curative agent, was first shown to be effective in leprosy in the 1940s, in studies at Carville, LA, USA, and was made available worldwide around 1950. Today dapsone is combined with rifampicin in 6- to 12-month regimens to treat forms of the disease with few bacilli ("paucibacillary").³ For patients with heavy bacterial infection ("multibacillary"), an additional agent, clofazimine, is used in 12- to 24-month regimens. Ofloxacin, clarithromycin, and minocycline are additional effective agents that can be substituted for the others when necessary, but they are more expensive.

Two strategies currently drive leprosy research and clinical efforts globally: the disease elimination approach, and a modern version of the older leprosy-control approach. These strategies share the objectives of developing methods for early diagnosis and, more ambitiously, of developing an effective vaccine. Elimination-driven programmes, however, place most emphasis on diagnosis and the delivery of antimicrobial treatment, and less emphasis on the long-standing consequences of leprosy. In contrast, the control-oriented approach places continued emphasis on the early identification of nerve impairment, prevention of disability, and better diagnosis and management of the acute inflammatory episodes called "reactions".

Developing a leprosy vaccine has been a consummate goal of leprosy research since the WHO's programme on the immunology of leprosy first promulgated the idea in the 1970s. Early efforts were not successful, and new attempts still face both technical challenges (designing a vaccine to elicit cellular immunity), and operational challenges (who would be

vaccinated?). Current efforts are focused on identifying unique, immunogenic antigens, then incorporating the appropriate antigen into a multivalent vaccine against tuberculosis and other, more highly prevalent pathogens.⁴

M. leprae has still not been cultivated. The full genome has been sequenced,⁵ however, so that microbiologists can now study many previously inaccessible aspects of its function. The genome of *M. leprae* is substantially smaller than that of *M. tuberculosis*, and pseudogenes account for nearly 50% of *M. leprae*'s total genome, a near record in microbiology. Many important metabolic pathways are now known to be absent or non-functional in *M. leprae*. Availability of its genetic sequence has also led to promising advances in the identification of strains of this organism, based on assessment of short tandem repeat sequences in the genome.⁶

The uniquely broad spectrum of cellular immune responses to *M. leprae* have challenged immunologists since the immunological basis of the diversity in leprosy was first recognised in the 1960s.^{7,8} In the last 2 decades, the diversity of lesions has been described in increasing detail with respect to the participation of different T-lymphocyte subsets and cytokine production. However, these advances in cellular and molecular immunology have still not explained how this non-cultivable, exceptionally slow growing and well adapted pathogen can elicit such a wide range of cellular immune responses.³

Evidence now suggests that resistance to leprosy is controlled genetically at 2 levels. At the first, "innate-resistance" level, certain genes are associated with overall resistance/susceptibility to leprosy.⁹ For susceptible individuals, other specific genes regulate the nature and degree of the cellular immune response.¹⁰ It is likely that major new directions in research for leprosy diagnosis and treatment will be stimulated by these discoveries in genetics.

Neuritis and reactions are the other two major clinical challenges in leprosy. Leprosy is the leading infectious cause of crippling, due to its unique ability to infect peripheral nerves. At least some nerve involvement occurs very early in this disease, since the diagnostic feature of early skin lesions is central hypoesthesia or anaesthesia. Widespread use of sensitive, quantitative measurements of sensory capability has advanced clinical and epidemiological understanding of nerve function impairment,¹¹ and has allowed quantitative comparisons of the results of different regimens of corticosteroid therapy.¹²

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However, studies of the mechanisms underlying neuritis in leprosy have lagged behind, due to the inability to biopsy the affected nerves to examine them directly and the lack of animal models.³ Available evidence, however, suggests that *M. leprae* probably enter peripheral nerves via their blood supply, and ultimately they infect Schwann cells. The bacilli apparently thrive within these cells, but the extent to which they alter myelination and other Schwann cell functions is not known because of conflicting evidence in vitro. Immunological and inflammatory processes similar to those observed in the skin also occur in and around nerves; in patients with a high degree of cellular immunity to *M. leprae*, they may cause granulomatous destruction of the nerve.

Segmental demyelination occurs in some nerves, and axonal atrophy has also been described. However, the mechanisms, interrelations, and even the sequence of these processes are not clearly understood. The nine-banded armadillo is an established model of leprosy neuritis,¹³ and is the focus of extensive research to better understand the mechanisms of nerve injury in leprosy. Such research is desperately needed because neuropathy is the major contributor to the long-term physical, psychological, and social debility of this disease.

Reactions are acute inflammatory episodes that are superimposed upon the chronic inflammation of leprosy. They occur in about 40% of patients, are major contributors to morbidity, and should be regarded as medical emergencies because of the risk of rapid, serious nerve injury. Reactions are major challenges to treatment because their mechanisms are not well understood and no laboratory tests can determine their severity, or the effectiveness of treatment, including the termination of the reaction.

Two types of reactions are seen worldwide. Type 1 (“reversal”) reactions, seen in patients with borderline leprosy, are characterised by exacerbation of previously existing lesions, which become erythematous and indurated, often accompanied by acute neuritis. Substantial evidence indicates that Type 1 reactions result from spontaneous enhancement of cellular immunity, but the factors precipitating this flare, and the mechanisms involved, are not understood. Notably, Type 1 reactions may appear as an immune reconstitution inflammatory phenomenon in patients whose immunity has been compromised by AIDS,¹⁴ or by inhibitors of TNF α ,¹⁵ after reversal of the immunosuppression. Type 1 reactions often require prolonged treatment with high doses of corticosteroid to prevent or reduce neuritis, and current therapeutic trials of several other agents attempt to identify corticosteroid-sparing regimens.^{3,16}

Type 2 reactions (erythema nodosum leprosum, ENL), in patients with lepromatous leprosy, are characterised by the sudden development of crops of tender, red nodules anywhere on the body, irrespective of prior lesions; they are also often accompanied by neuritis. The mechanism underlying ENL reactions is not known but, based on circumstantial evidence, they are usually ascribed to immune complexes.³ The factors that precipitate Type 2 reactions are also unknown. These reactions usually respond extraordinarily well to thalidomide,

and it is this benefit that kept thalidomide from being totally banned after its teratogenicity was recognised. The mechanism by which thalidomide exerts its remarkable effect on these reactions remains controversial.¹⁷ Because the use of thalidomide is highly controlled, most patients with Type 2 reactions are first treated with corticosteroids. Some patients are beset by recurrent Type 2 reactions and, as with Type 1 reactions, management of these patients with prolonged, high-dose corticosteroids entails many risks and side effects.

In 2008, infection with *M. leprae* is curable, but it is still a serious global problem. Early diagnosis and prevention of this infection, and of its complications – neuropathy and leprosy reactions – continue to pose serious challenges to physicians and scientists alike.

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