Seminar

Leprosy

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Leprosy remains an important health problem worldwide. The disease is caused by a chronic granulomatous infection of the skin and peripheral nerves with *Mycobacterium leprae*. The clinical range from tuberculoid to lepromatous leprosy is a result of variation in the cellular immune response to the mycobacterium. The resulting impairment of nerve function causes the disabilities associated with leprosy. This review summarises recent advances in understanding of the biology of leprosy, clinical features of the disease, the current diagnostic criteria, and the new approaches to treatment of the infection and the immune-mediated complications. Supervised multi-drug therapy (MDT) for fixed durations is highly effective for all forms of the disease. The widespread implementation of MDT has been associated with a fall in the prevalence of the leprosy but as yet no reduction in the case-detection rate globally. Thus, leprosy control activities must be maintained for decades to interrupt transmission of infection.

Leprosy is a chronic granulomatous infection of the skin and peripheral nerves with the intracellular bacterium *Mycobacterium leprae*. The damage to peripheral nerves results in sensory and motor impairment with characteristic deformities and disability. Leprosy was once widely distributed in Europe and Asia but now occurs mainly in resource-poor countries in tropical and warm temperate regions. However, patients may present with the disease long after leaving an endemic region, and clinicians must be able to recognise it. The fact that the organism cannot be grown in culture has hindered studies in vitro, and clinical trials are difficult in this slowly progressive, chronic infection. Over the past 5–10 years, however, there have been major advances in understanding of the biology of both *M leprae* and the host response to the organism, and more than 11 million patients have been treated with multi-drug therapy (MDT).[1,2] Currently, leprosy control is being integrated into general health care, which offers new challenges if leprosy patients are to be detected and their disease managed appropriately.

Epidemiology of leprosy

During the 1990s a bold, ambitious leprosy elimination campaign was launched, after the adoption by the World Health Assembly of the goal of the "elimination of leprosy as a public health problem by the year 2000".[3] Elimination was defined as a reduction in the prevalence of leprosy patients receiving antimicrobial therapy to less than 1 per 10 000 population. The rationale for this definition lay in the recognition that combination antibiotic therapy was highly effective and the assumption that once the pool of infectious patients was reduced, the disease would gradually disappear. However, there was no evidence that achievement of the arbitrarily chosen prevalence would reduce transmission of *M leprae*.[4,5] MDT was developed in response to the widespread emergence of dapsone resistance[6] and was based on effective combinations of antibiotics in experimental leprosy infection.[7] The MDT regimens were very effective both for individual patients and in leprosy control programmes and were widely implemented. In 1985, there were an estimated 12 million people with leprosy worldwide, a prevalence of 12 per 10 000. In 2002, WHO reported that there were 597 000 registered cases and 719 000 new cases detected during 2000, resulting in a global prevalence of registered leprosy patients of just below 1 per 10 000.[2,8] 15 endemic countries still have a prevalence of more than 1 per 10 000, mainly in Asia, Africa, and South America, but 107 of the 122 countries endemic for leprosy in 1985 have reached the elimination target. There is a concentration of 83% of the registered cases in only six countries: India, Brazil, Burma, Indonesia, Madagascar, and Nepal, with India accounting for 64% of all leprosy cases worldwide (table 1). Leprosy also shows clustering to limited geographical regions or ethnic groups within a country.[9–12]

As a result of this outstanding public-health achievement, more than 11 million people with leprosy have been cured by MDT, many without any disability. The fall in the prevalence of leprosy has not, however, been accompanied by a fall in the rate of detection of new cases (figure 1). The observed fall in the prevalence could have been largely caused by shortening of the duration of treatment (see below) and the removal from the registers of cured or defaulted patients, rather than a reduction in the transmission of *M leprae* infection. The true incidence

Search strategy and selection criteria

Papers for this review were identified by searches of MEDLINE and PubMed with the search terms "*Mycobacterium leprae*", "leprosy", "immunology", "leprosy reactions", and "treatment" from 1993 to December, 2002. Only papers published in English were considered. Furthermore, we both identified any new work of relevance reported at the International Leprosy Congress in Salvador, Brazil, in August, 2002. DL was a member of the International Leprosy Association Technical Forum that undertook a systematic review of publications on leprosy diagnosis.[4]

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	Prevalence (per 10 000)*	Case detection (per 100 000)†	% of cases multibacillary‡	% of cases in children	% with disability (grade 2)
Country					
India	384 240 (3·8)	559 938 (55·2)	34	2	2
Brazil	77 676 (4·6)	41 070 (24·1)	NA	NA	NA
Burma	10 389 (2·3)	10 286 (22·6)	53	9	7
Madagascar	8662 (5·4)	8445 (53·0)	60	14	8
Nepal	7984 (4·0)	8020 (34·4)	58	7	8
Mozambique	7834 (4·0)	6617 (4·0)	65	12	14
Total	496 785 (3·9)	634 376 (49·2)	35	3	3

NA=not available. *Number of leprosy cases registered at the end of 2000 (rate per 10 000).[2] †Number of new leprosy cases detected during 2000 (rate per 100 000).[2] ‡Proportion of new cases with >5 skin lesions.

Table 1: **Prevalence and case detection of leprosy in the six endemic countries with the highest leprosy burden during 2000 and the proportions of the new cases in children and cases with multibacillary disease and disability**

of leprosy disease is difficult to measure, and the rate of leprosy infection in a community cannot be measured, by contrast with tuberculosis, for which the annual rate of *M tuberculosis* infection is estimated from surveys of tuberculin skin-test reactivity. Therefore the actual case-detection rate provides the most helpful estimate of leprosy burden,[13] and it has increased during the past 10 years (figure 1).[2,4] The rise in the annual case-detection rate could reflect improved leprosy control and case-finding activities in endemic countries, rather than an increase in leprosy incidence. Further observation is needed to show whether long-term implementation of MDT programmes leads to the predicted fall in the incidence of leprosy disease.

The main consequence of leprosy infection for patients is the disability secondary to impairment of nerve function. The proportion of new patients with visible disability, such as skin ulceration or muscle wasting and contracture, varies between countries (table 1) and is affected by the type of leprosy and delay in diagnosis. An estimated 3 million leprosy patients have completed MDT and have sustained disability from nerve damage; these patients need continuing care to limit further secondary damage.[4]

Leprosy shows a wide range of clinical presentations from tuberculoid through borderline forms to lepromatous (figure 2), classified by Ridley and Jopling[14] largely on pathological grounds, but later confirmed by immunological analysis (see below). The incubation period between infection and overt disease varies widely from months to 30 years, and the mean is estimated to be 4 years for tuberculoid and 10 years for lepromatous leprosy.[15] A low rate of leprosy transmission can continue for many decades, as shown by the appearance of new cases in regions of South Africa with longstanding control programmes.[9] There is a male predominance in leprosy patients after the age of puberty, with a male to female ratio of 1·5–2·0 to 1. This difference is real and is not related to underdiagnosis in women, although in some countries it is accentuated by delayed presentation by female patients, which results in higher rates of deformity.[16]

The principal means of transmission of *M leprae* is probably by aerosol spread of nasal secretions and uptake through nasal or respiratory mucosa.[15] *M leprae* cannot traverse intact skin in either direction, and the infection is not spread by touching. Acid-fast mycobacteria and *M leprae* DNA are found in the nasal secretions of patients with lepromatous leprosy.[17] *M leprae* DNA can also be detected in nasal swabs from up to 5% of healthy individuals in India and Indonesia, which suggests that subclinical infection occurs more frequently in these areas than previously thought.[17,18] Subclinical infection can also be detected by the development of specific T-cell[19] and antibody responses to *M leprae*.[11] Most individuals with subclinical infection do not develop clinical disease. Proximity to leprosy patients is an important determinant of transmission.[15,20] The relative risk for leprosy disease in household contacts is 8–10 for lepromatous disease and 2–4 for tuberculoid forms.[15] As leprosy prevalence falls in a community, the relative importance of household transmission increases; this association might justify prophylactic therapy in family or other close contacts of leprosy patients.[21]

Immunity against *M leprae* depends on intact T-cell function, but in contrast to tuberculosis, coinfection with HIV has no strong effect on the development of clinical leprosy.[22] Contrary to expectations early in the HIV epidemic, case-control studies[23–25] have shown that HIV-1 infection is not a risk factor for leprosy. Patients coinfected with HIV and leprosy have typical skin lesions and the usual patterns of leprosy histology and granuloma formation, even in the presence of low numbers of circulating CD4-positive T cells, and are at continued risk of developing immune-mediated reactions.[26] Immune reactions can also develop as part of an immune-reconstitution process in leprosy/HIV-coinfected patients starting highly active antiretroviral therapy.[27]

Biology of *M leprae*

The completion of the genomic sequence of *M leprae* is a major advance,[28] which will assist in elucidation of the unique biology of the organism. Previously, detailed studies on *M leprae* were prevented by the inability to grow the mycobacteria in culture. *M leprae* is an acid-fast gram-positive bacillus and an obligate intracellular

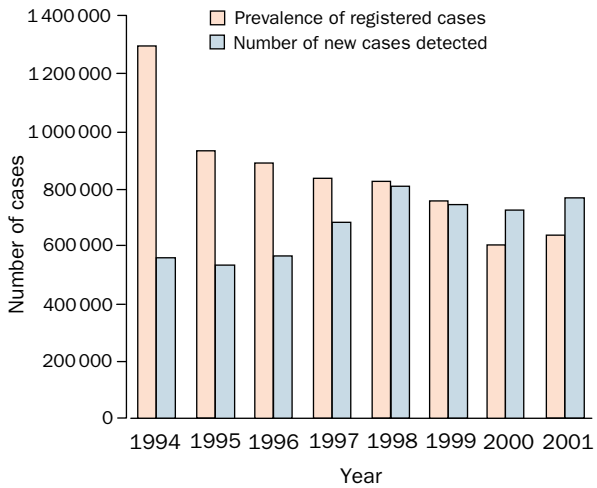

Figure 1: **Prevalence of registered leprosy patients receiving antimicrobial therapy at the end of each year and the number of new cases detected during the year reported to WHO for the period 1994–2001[2,8]**

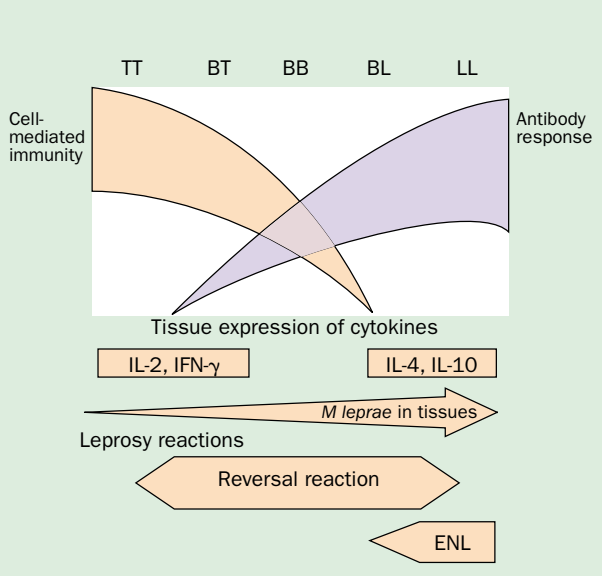

Figure 2: **Clinical-immunopathological range of leprosy**
IL=interleukin; IFN=interferon; ENL=erythema nodosum leprosum.

parasite with tropism for macrophages and Schwann cells. The bacilli show preference for growth in cooler regions of the body. The organism can replicate in the mouse footpad[29] and the nine-banded armadillo,[30] which have provided bacteria for study. The *M leprae* genome includes 1605 genes encoding proteins and 50 genes for stable RNA molecules.[28] More than half of the functional genes in the *M tuberculosis* genome are absent and have been replaced by many inactivated genes or pseudogenes. *M leprae* seems to have jettisoned genes normally required for replication ex vivo and assumed a unique ecological niche with a very limited host range and the need for growth within cells. This gene decay has removed entire metabolic pathways and regulatory genes, particularly those involved in catabolism, but the genes essential for the formation of a mycobacterial cell wall have been retained.[31] The leprosy bacillus might therefore be dependent on host metabolic products, which could explain its long generation time and inability to grow in culture.[28] Future comparative analysis of the genomes of *M leprae* and other mycobacteria might reveal the molecular basis for the slow rate of replication and dependence on host cells for growth of *M leprae*. There appears to be limited genetic diversity in *M leprae*, less than in *M* tuberculosis,[32] and there is no evidence that the observed genetic variations influence the virulence of *M leprae*.[33,34]

The mycobacterial cell wall contains important targets of the host immune response. These include the species-specific phenolic glycolipid I (PGL-I), which stimulates a potent IgM antibody response[35] that is in proportion to the bacterial load in patients and falls with therapy.[36,37] Other components include lipoarabinomannan, which modulates macrophage bactericidal activities,[38] and proteins involved in cell-wall synthesis. Cell-wall proteins purified free of the immunomodulatory glycolipid components are potent T-cell antigens, which stimulate protective immunity in murine *M leprae* infection.[39] The genes for various protein antigens[40] have been identified, including antigens shared with *M tuberculosis*[41–43] and others shared only with environmental mycobacteria.[44,45] Both types of antigen can induce protective immunity against *M leprae*.[46,47] The *M leprae* genome includes several novel open reading frames not present in *M tuberculosis*.[28] These proteins restricted to *M leprae* might provide the basis for specific skin tests and other diagnostic assays to detect infection with the mycobacterium.[48,49]

The unique predilection of *M leprae* for Schwann cells is probably determined by the mycobacterium's binding to the G domain of the α2 chain of laminin 2, which is a component of the basal lamina of Schwann cells.[50] This form of laminin is restricted to peripheral nerves, which explains the specific tropism of *M leprae*. The subsequent uptake of *M leprae* by the Schwann cell depends on α-dystroglycan, which is the receptor for laminin within the cell membrane, and other intracellular components.[51] Several candidate molecules on the surface of *M leprae* bind to this complex, including the specific terminal trisaccharide of PGL-I and a 21 kDa protein;[52,53] however, the specificity of these interactions has not been fully resolved.[54] Once inside the Schwann cell, the leprosy bacilli replicate slowly over years. At some stage, specific T cells recognise the presence of mycobacterial antigens within the nerve and initiate a chronic inflammatory reaction. The Schwann cells can express HLA class 2 molecules and play an active part in the immunological reaction by presenting mycobacterial peptides to HLA-class-2-restricted CD4-positive T cells.[55] Swelling within the inflexible perineurium leads to ischaemia, further nerve damage, and eventually fibrosis with axonal death.[56]

Host response

Host genetic factors have a partial effect on both the development of leprosy and the pattern of disease. Whole-genome screening has identified susceptibility loci on chromosome 10p13, close to the gene for the mannose receptor C type 1, a phagocytic receptor on macrophages, and on chromosome 6 within the MHC.[57] Within this region linkage has been shown to HLA class II genes in Indian patients with leprosy and to the gene for tumour necrosis factor (TNF) in Brazilian patients.[58] Polymorphisms in the promoters for genes for both TNF and interleukin 10 are associated with the development of leprosy,[59] and particularly with multibacillary leprosy in the case of the TNF promoter polymorphisms.[60] The HLA locus also affects the pattern of disease: HLA DR2 and DR3 alleles are associated with tuberculoid disease, and HLA DQ1 is linked to lepromatous leprosy.[61] A mutation in the toll-like receptor 2 (TLR2) gene is more common in patients with lepromatous leprosy than in those with other forms in Korea, which suggests that this TLR2 signalling contributes to susceptibility.[62] Polymorphisms in the *NRAMP1* gene are associated with multibacillary leprosy in African patients,[63] and this gene has also been linked with cellular immunity to *M leprae*.[64]

The varying clinical forms of leprosy[14] are determined by the underlying immunological response to *M leprae* (figure 2). At one pole, patients with tuberculoid leprosy (TT) have a vigorous cellular immune response to the mycobacterium, which limits the disease to a few well-defined skin patches or nerve trunks.[65] The lesions are infiltrated by interferon-γ-secreting CD4-positive T lymphocytes,[66] which form well-demarcated granulomas, containing epithelioid and multinucleate giant cells, around dermal nerves. Few, if any, acid-fast mycobacteria can be found in the lesions. Strong cellular immunity is confirmed by T-cell proliferative and cytokine responses to *M leprae* antigens in vitro and by skin-test reactivity to soluble preparations of *M leprae* and to dead whole *M leprae* organisms (Mitsuda reaction). Antibody responses to *M leprae* antigens are absent or weak. At the other pole, lepromatous leprosy (LL) is

characterised by the absence of specific cellular immunity but intact immunity to the related *M tuberculosis*. There is therefore uncontrolled proliferation of leprosy bacilli with many lesions and extensive infiltration of the skin and nerves. The dermis contains foamy macrophages filled with many bacteria, but few CD4-positive and CD8-positive T lymphocytes and no organised granulomas. There are high titres of antibodies to PGL-I and protein antigens specific for *M leprae*,[37,44] and mycobacterial antigens are readily identified in the urine and blood.[36] Most patients have the intermediate forms of borderline-tuberculoid (BT), mid-borderline (BB), and borderline-lepromatous (BL) leprosy. These forms are characterised by a progressive reduction from BT to BL leprosy in cellular responses, associated with an increasing bacillary load, more frequent skin and nerve lesions, and higher antibody titres. The borderline forms are clinically unstable, and patients either show slow change towards the lepromatous pole or experience sudden type I or reversal reactions.

Elucidation of the immunological basis of the leprosy clinical range and the T-cell unresponsiveness in lepromatous leprosy has been central to research on the disease. Possible explanations include immune deviation of the CD4-positive T-cell response, deletion of T cells reactive to *M leprae* in patients with lepromatous leprosy, and the presence of regulatory or suppressor T cells. Immune deviation is evident since skin and nerve lesions in tuberculoid leprosy are infiltrated by Th1-like T cells, which produce abundant interferon γ, TNFα, and interleukins 2 and 15 (T-cell growth factors).[66–68] Transcripts for interleukins 12 and 18, which are required for the development of Th1 T cells, are abundant in tuberculoid and borderline-tuberculoid skin lesions.[69,70] T cells from patients with tuberculoid, but not lepromatous, disease express interleukin-12 receptors and respond to stimulation with interleukins 12 and 18 in vitro.[70,71] By contrast, the lesions from patients with lepromatous disease contain mRNA for the Th2-like cytokines interleukins 4 and 10.[66] Peripheral-blood T cells or T-cell clones from some patients with borderline-lepromatous or lepromatous leprosy produce interleukins 4 and 10;[66] however, the T-cell responses are not completely deviated to the Th2 pattern, since a mixed Th0-like phenotype with concomitant expression of interleukins 4 and 10 and interferon γ can be detected in T cells from patients with lepromatous leprosy after stimulation with *M leprae*.[72,73] In some patients with this form, T cells responsive to *M leprae* cannot be demonstrated, which suggests that deletion has occurred. Another explanation is that there is active inhibitory or suppressor T-cell activity in lepromatous leprosy. Suppressor CD4-positive T-cell clones isolated from patients with lepromatous leprosy inhibit specific responses of other T-cell clones from the same patient.[74] The combination of recombinant interleukins 12 and 2 restores Th1 responses in lymphocytes from some patients with borderline-lepromatous or lepromatous disease, which suggests that the "inhibitory" effect is reversible.[75,76] A similar redirection of the cytokine production from a Th2-like to a Th1-like pattern was achieved by presenting *M leprae* in specialised dendritic cells to T cells from patients with lepromatous leprosy.[77] This finding has implications for vaccines and immunotherapy in leprosy. Indeed, immunisation with dead *M leprae* with BCG or viable mycobacterial vaccines can reverse the *M leprae* hyporesponsiveness in some, but not all, patients with borderline-lepromatous or lepromatous disease.

Analysis of the cellular responses in leprosy skin lesions has identified additional classes of T cells recruited to the site of infection, including T cells expressing γδ T-cell receptors[78] and the novel CD4-negative, CD8-negative (double negative) αβ T cells.[79] These T cells recognise non-peptide antigens, including mycobacterial lipoarabinomannin and mycolic acid, which are presented by CD1 molecules on antigen-presenting cells independent of HLA classes I and II.[79] CD1 proteins are strongly expressed on dendritic cells in dermal granulomas in patients with tuberculoid leprosy, but are not induced in the lesions of lepromatous leprosy, which suggests that CD1-restricted T cells contribute to the control of the pathogen.[80]

The dynamic nature of the immune response to *M leprae* leads to spontaneous fluctuations in the clinical state, which are termed leprosy reactions. Type 1 leprosy reactions or reversal reactions, which occur in a third of patients with borderline forms of disease, are caused by spontaneous increases in T-cell reactivity to mycobacterial antigens.[56] Reversal reactions are associated with the infiltration of interferon γ and TNFα-secreting CD4-positive lymphocytes in skin lesions and nerves, resulting in oedema and painful inflammation.[68,81] Cytokine production by peripheral-blood lymphocytes[82] and serum cytokine concentrations[83] are also increased during reversal reactions. They fall with corticosteroid treatment, but patients with high cytokine responses have a poor clinical response to treatment and are more likely to relapse after withdrawal of corticosteroid therapy.[82] The poor outcome emphasises that rapid and sustained reversal of the inflammatory process in type 1 reactions is essential to prevent continuing nerve damage.

Type 2 reaction or erythema nodosum leprosum (ENL) is a systemic inflammatory response to the deposition of extravascular immune complexes leading to neutrophil infiltration and activation of complement in many organs.[84] This reaction is accompanied by high circulating concentrations of TNFα[83] and striking systemic toxicity. ENL occurs only in borderline-lepromatous and lepromatous leprosy.

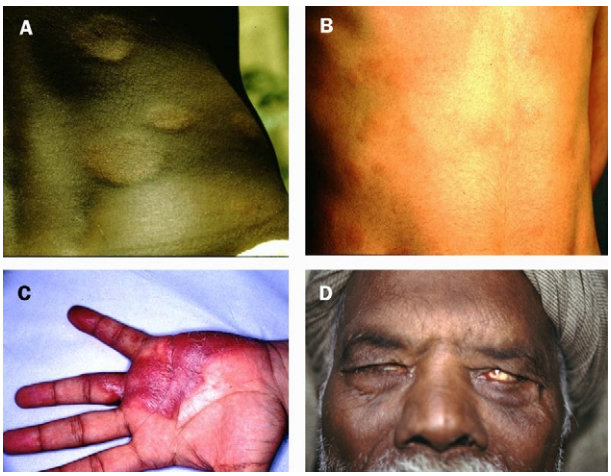

Figure 3: **Leprosy appearance**
A: Borderline-tuberculoid leprosy—many, clear-edged, anaesthetic lesions on the trunk and buttocks; the bacterial index (BI) on skin smear was 1. B: Lepromatous leprosy—widespread, non-anaesthetic plaques and early nodules; BI=4. C: Borderline-tuberculoid leprosy in reversal reaction—the patient has two lesions on his hand and a tender painful ulnar nerve; the skin lesions had been anaesthetic and had recently become erythematous; BI=0. D: bilateral lagophthalmos secondary to the involvement of the VIIth nerve with leprosy.

Clinical features of disease

Leprosy affects skin, nerves, and eyes, and causes systemic features in lepromatous disease. Patients commonly present with skin lesions, weakness or numbness caused by a peripheral-nerve lesion, or a burn or ulcer in an anaesthetic hand or foot. Borderline patients may present in leprosy reactions with nerve pain, sudden palsy, many new skin lesions, eye pain, or a systemic febrile illness.

Skin involvement

The commonest skin lesions are macules or plaques; more rarely papules and nodules are seen.[65] Lesions are hypopigmented in borderline-tuberculoid and tuberculoid leprosy and infiltrated with a raised edge (figure 3). On pale skins, lesions can appear erythematous. In lepromatous leprosy, diffuse infiltration of the skin commonly occurs. Patients with tuberculoid disease have few, hypopigmented lesions with reduced sensation, whereas those with lepromatous forms have many lesions, confluent in some cases, and many of them are not hypoaesthetic (figure 3). Inspection of the whole body in good light is important because otherwise lesions might be missed, particularly on the buttocks in borderline disease. Skin lesions should be examined for hypoaesthesia to light touch, pin-prick, and temperature and for anhidrosis.

Nerve damage

Damage to the nerves occurs in two settings—peripheral nerve trunks and small dermal nerves. Peripheral nerves are affected in fibro-osseous tunnels near the surface of the skin, including the great auricular nerve (neck), ulnar nerve (elbow), radial-cutaneous nerve (wrist), median nerve (wrist), lateral popliteal nerve (neck of the fibula), and posterior tibial nerve (medial malleolus). The posterior tibial nerve is the most commonly affected, followed by the ulnar, median, lateral popliteal, and facial nerves.[85,86] Involvement of these nerves produces enlargement, with or without tenderness, and standard regional patterns of sensory and motor loss. Small dermal sensory and autonomic nerves are affected producing hypoaesthesia and anhidrosis within borderline-tuberculoid and tuberculoid lesions and glove and stocking sensory loss in lepromatous disease. Sensation on the hands and feet can be assessed and monitored by use of Semmes-Weins monofilaments.[87]

Pure neuritic leprosy presents with asymmetrical involvement of peripheral nerve trunks and no visible skin lesions. Histology of a cutaneous-nerve biopsy sample might reveal any type of leprosy.[88] This form is seen most frequently, but not exclusively, in India and Nepal, where it accounts for 5–10% of patients.[89,90]

Systemic features

These features are seen mainly in lepromatous patients and are due to bacillary infiltration affecting nasal mucosa, bones, and testes.[91] Testicular atrophy results from diffuse infiltration and the acute orchiitis that occurs with ENL reactions. The consequent loss of testosterone leads to azoospermia and gynaecomastia. Renal involvement and amyloidosis are now rarely seen with effective MDT.

Eye involvement

Blindness resulting from leprosy is devastating for a patient with anaesthetic hands and feet. Eye damage results from both nerve damage and direct bacillary invasion. A recent cohort study found that 2·8% of multibacillary patients were blind at diagnosis and a further 11% had potentially blinding ocular pathology.[92]

Diagnostic signs of leprosy

- Hypopigmented or reddish patches with definite loss of sensation
- Thickened peripheral nerves
- Acid-fast bacilli on skin smears or biopsy material

Lagophthalmos results from paresis of the orbicularis oculi caused by involvement of the zygomatic and temporal branches of the facial (VIIth) nerve (figure 3). Facial lesions are associated with a ten-fold increase in the risk of facial nerve damage.[93] In lepromatous disease lagophthalmos occurs later and is bilateral in most cases. Damage to the ophthalmic branch of the trigeminal (Vth) nerve causes anaesthesia of the cornea and conjunctiva, which results in a dry, insensitive cornea and a reduction in blinking. These effects leave the cornea at risk of minor trauma and ulceration.

Diagnostic criteria for leprosy

Diagnosis of leprosy is clinical and is based on patients having one or more of three cardinal signs (panel).[1] The reliability of these signs has been extensively reviewed.[4] In Ethiopia, use of these three criteria resulted in sensitivity of 97% with a positive predictive value of 98% for the diagnosis of leprosy.[4] In Bangladeshi and Ethiopian cohorts of patients, 96% and 91% of patients with multibacillary disease and 86% and 76% of those with paucibacillary disease had enlargement of one or more nerves.[94,95] Skin smears, taken to detect intradermal acid-fast bacilli, have high specificity, but low sensitivity, because about 70% of all leprosy patients are smear negative.[5] Nevertheless, skin smears are important because they identify the most infectious patients and those at greatest risk of relapse. Histological diagnosis, when available, is deemed the gold standard for diagnosis. The presence of neural inflammation histologically differentiates leprosy from other granulomatous disorders.

The proposal that leprosy might be diagnosed by the presence of an anaesthetic skin lesion alone does not pass critical assessment.[4] Although 70% of leprosy skin lesions have reduced sensation, the non-anaesthetic 30% of lesions occur in patients with multibacillary disease,[96] who are infectious and have a higher risk of developing disability than those with paucibacillary disease. Therefore the other criteria should also be used.

Outside leprosy-endemic areas the diagnosis of leprosy is commonly not considered. Of new leprosy patients seen during 1995–99 at the Hospital for Tropical Diseases in London, UK, diagnosis had been delayed in more than 80% of cases, despite review by dermatologists, neurologists, orthopaedic surgeons, and rheumatologists.[97] These delays had serious consequences for patients, with over 50% having nerve damage and disability. Leprosy should be considered as a cause of peripheral neuropathy or persistent skin lesions in patients from leprosy-endemic countries.

Classification of disease

Classification of patients according to the Ridley-Jopling scale[14] is clinically useful. Borderline-tuberculoid leprosy can be associated with rapid and severe nerve damage, whereas lepromatous disease is associated with chronicity and long-term complications. Borderline disease is unstable and can be complicated by reactions. There is also a simpler field classification determined by the number of skin patches: single skin lesion (one patch), paucibacillary (two to five patches), and multibacillary

(more than five patches). Patients with multibacillary leprosy are more likely than those with the other forms to develop reversal reactions and impairment of nerve function.[98]

Serology and PCR for diagnosis

A simple diagnostic test to support the diagnosis of paucibacillary leprosy would be useful. Neither serology nor PCR has a role for this at present.[4] Antibodies to the *M leprae* specific PGL-I are present in 90% of patients with untreated lepromatous disease, but only 40–50% of patients with paucibacillary disease, and 1–5% of healthy controls.[37,99] PCR for detection of *M leprae* DNA encoding specific genes or repeat sequences is potentially highly sensitive and specific, since it detects *M leprae* DNA in 95% of multibacillary and 55% of paucibacillary patients.[100,101] Currently PCR is not used in clinical practice.

Treatment of leprosy

Chemotherapy

The first-line drugs against leprosy are rifampicin, clofazimine, and dapsone. All patients should receive a multidrug combination with monthly supervision (table 2). Current controversies focus on the length of treatment, the mode of treatment, and relapse rates. Dapsone was the first effective antimicrobial agent against *M leprae*.[65] The multidrug combinations were introduced without formal clinical trials in the 1982 when rates of primary and secondary dapsone resistance of 30% were reported.[102] Since then multiple-drug-resistant organisms have not arisen; however, there has been little standard monitoring of clinical outcomes and relapse rates. The few studies of drug sensitivity in patients relapsing after MDT have shown that relapse occurred with drug-sensitive *M leprae*.[103] Dapsone resistance is associated with missense mutations in the *folP1* gene encoding dihydropteroate synthase,[104,105] and these mutations can be identified by a PCR assay that detects the presence of *M leprae* in skin biopsy material and its susceptibility to dapsone.[106]

Rifampicin is a potent bactericidal for *M leprae*. 4 days after a single 600 mg dose, bacilli from a previously untreated multibacillary patient are no longer viable in the mouse footpad test.[107] Rifampicin acts by inhibiting the DNA-dependent RNA polymerase, and resistance is due to mutations in a small region of *rpoB*.[108] This feature permitted the development of a PCR-based assay for detecting rifampicin resistance in *M leprae* organisms in clinical samples without the need for the long mouse footpad assay.[109] Because *M leprae* resistance to rifampicin can develop as a one-step process, the drug should always be given in combination with other agents against leprosy.[109] In untreated lepromatous patients, a single monthly dose of rifampicin (1200 mg) plus daily dapsone was as effective as daily rifampicin (450 mg) plus dapsone;[110] thus, monthly rifampicin is satisfactory therapy.

Clofazimine has a weakly bactericidal action, the mechanism of which is unknown. It also has an anti-inflammatory effect that has reduced the incidence of ENL reactions.[84] Skin discolouration is the most troublesome side-effect, ranging from red to purple-black. The pigmentation fades slowly in most cases after withdrawal of clofazimine. This drug also produces a characteristic icthyosis on the shins and forearms.

Published clinical outcomes for patients treated with the paucibacillary regimen show that 2–44% of patients have clinically active skin lesions at the end of 6 months of treatment.[5] Nerve impairment occurred de novo in 2·5% of patients, and visible disabilities increased from 4% at enrolment to 7% after 8–10 years of follow-up. Relapse rates in paucibacillary leprosy are low, ranging from zero in Ethiopia[111] to 2·5% over 4 years in Malawi.[112]

One study in Thailand found that in patients treated with the multibacillary regimen for 24 months, 29% of skin lesions were still active after 3 years and that visible disabilities increased from 5% at enrolment to 13% at 8–10 years of follow-up.[113] Relapse rates reported from six observational studies range from zero in China and Ethiopia to 2·04 per 100 person-years in India.[5] Data from west Africa[114] and India[115] show that patients with a high initial bacterial load (bacterial index 4) treated with rifampicin, clofazimine, and dapsone for 2 years had a relapse rate of 8 per 100 person-years, whereas patients treated to smear negativity had a relapse rate of 2 per 100 person-years. These patients with a high bacillary load could be a subgroup who need treatment until skin smear negativity.[116]

Minocycline, the macrolide clarithromycin, and the fluoroquinolones pefloxacin and ofloxacin are all highly active against *M leprae* in mouse footpad infection and in patients,[117] but because of their cost are rarely used in field programmes. They can, however, be used as second-line drugs in the case of dapsone allergy[1] or if clofazimine pigmentation is challenging for the patient. Minocycline can also cause a long-lasting grey-black pigmentation of active leprosy lesions.[118]

The recommended duration of treatment for multibacillary patients has lately been reduced from 24 months to 12 months.[1] There was no evidence from controlled trials to guide this decision, but the classification of multibacillary patients had been widened so that some patients who previously would have received paucibacillary treatment from 6 months were now receiving multibacillary treatment for 12 months. The effect of this change requires continuing assessment. New proposals include a clinical trial to test a common 6-month regimen of dapsone, clofazimine, and rifampicin for all leprosy patients.[12] This approach would simplify leprosy treatment but might cause problems because the regimen would significantly undertreat patients with a high bacterial load and would treat 60% of patients with a third drug that they do not require.[5]

The place of the drug combination rifampicin, ofloxacin, and minocycline is also unclear. It was recommended for single skin lesions[1] (table 2), but it is less effective than the 6-month paucibacillary MDT regimen.[119] Monthly doses of this regimen have been used in both paucibacillary and multibacillary disease with good clinical responses.[120] Although there may be a good initial response to rifampicin, ofloxacin, and minocycline, the important issue is the relapse rate over the next 10 years; careful long-term studies are needed before this

Type of leprosy*	Drug treatment		Duration of treatment (months)
	Monthly supervised	Daily, self administered	
Paucibacillary	Rifampicin 600 mg	Dapsone 100 mg	6
Multibacillary	Rifampicin 600 mg, clofazimine 300 mg	Clofazimine 50 mg, dapsone 100 mg	24
Paucibacillary single lesion	Rifampicin 600 mg, ofloxacin 400 mg, minocycline 100 mg		Single dose

*WHO classification[1] for field use when slit skin smears are not available. In field control programmes, WHO recommends treatment of multibacillary patients for 12 months only.[1]

Table 2: **Modified WHO-recommended MDT regimens**

treatment is extended. At this point use of the WHO regimens is recommended, since they are supported by 20 years of experience.

Monitoring and treatment of nerve damage

Impairment of nerve function can occur before diagnosis and during or after MDT. It can develop during a reaction or without overt signs of nerve or skin inflammation (silent neuropathy). In field cohort studies, 16–56% of newly diagnosed patients had impairment of nerve function.[121] In a Bangladeshi study, 25% of multibacillary patients developed nerve damage during treatment.[122] Patients at the highest risk of impairment of nerve function during and after treatment are those with multibacillary leprosy, pre-existing impairment of nerve function, or both features, and such patients ideally should be under surveillance for 2 years from diagnosis.[98] Analysis from a large cohort study in Ethiopia showed that standard nerve-function testing was needed monthly to detect new nerve damage early.[86]

Management of reactions and neuritis

Reversal reactions (type 1 reactions) manifest clinically with erythema and oedema of skin lesions and tender peripheral nerves (figure 3). Loss of nerve function can be dramatic. The peak time for reversal reactions is in the first 2 months of treatment, but they can continue to occur for 12 months, and occasionally after MDT is completed.[56,122] The treatment of reactions is aimed at controlling acute inflammation, easing pain, reversing nerve and eye damage, and reassuring the patient. MDT should be continued. Neuritis (nerve tenderness, new anaesthesia, and/or motor loss) or moderately inflamed skin lesions should be treated with corticosteroids. Standard courses of prednisolone have been used, starting at 40–60 mg daily, decreasing by 5 mg every 2–4 weeks after evidence of improvement.[56,123] Patients with borderline-tuberculoid reactions commonly need corticosteroids for 3–4 months, whereas those with borderline-lepromatous reactions may need treatment for 6 months. Inflammation is slow to settle, and even after 6 months of steroid treatment some patients still have high concentrations of proinflammmatory cytokines in their skin lesions.[68] In a recent Indian study different starting doses (60 *vs* 30 mg) and durations of therapy (12 *vs* 20 weeks) were compared; the longer duration of treatment gave the best outcomes (Sundar Rao PSS, personal communication). The expected recovery rate for nerve function is 60–70%. Recovery is less in patients with pre-existing impairment of nerve function or with chronic or recurrent reactions.

A different approach is to prevent the development of reversal reactions.[124] The feasibility of this approach was tested in a randomised controlled trial in multibacillary patients who received prednisolone (20 mg daily for the first 3 months and tapered for the 4th month) or placebo. There had been significantly fewer reactional episodes in the prednisolone-treated group at the end of treatment, but the protective effect was lost at the end of 12 months.[125] These studies show that reversal reactions are difficult to prevent and to switch off once established. Other established immunosuppressant drugs might have a role in treating reactions. In a pilot study in Nepal, patients had equivalent outcomes whether treated with an azathioprine/prednisolone combination or prednisolone alone.[126] Ciclosporin has also been used to treat reactions[56] and was effective in reducing skin and nerve inflammation; however, patients relapsed when the drug was withdrawn.[127]

Silent neuropathy should be treated similarly to reversal reactions, with prednisolone 40 mg daily and reducing over 4 months. Response rates vary according to the severity of initial damage, but even promptly treated nerve damage will improve in only 60% of cases.[122]

ENL (type 2 reactions) occur in about 20% of lepromatous and 10% of borderline-lepromatous patients, and patients with skin infiltration and bacterial index of 4 or more are at increased risk.[128] Patients are febrile with crops of small pink skin nodules; other signs are iritis, neuritis, lymphadenitis, orchiitis, bone pain, dactylitis, arthritis, and proteinuria. ENL can start during the first or second year of antimicrobial therapy and can relapse intermittently over several years. It is difficult to treat, necessitating repeated courses of corticosteroids.[84] Clofazimine has a useful anti-inflammatory effect in ENL and can be used at 300 mg daily for several months. Other agents have targeted the overproduction of TNFα that occurs in this disorder.[83] Thalidomide (400 mg daily) is better than steroids in controlling ENL and is the drug of choice for young men with severe ENL.[129] Use of thalidomide in women with severe ENL is a difficult decision for the woman and her physician, and careful discussion of the benefits and risks, particularly phocomelia when thalidomide is taken in the first trimester, is needed. Pentoxifylline, which inhibits TNFα production, has been used to treat ENL but was inferior to both thalidomide and steroids.[130] Neutralisation of TNFα with monoclonal antibodies or soluble inhibitors, as used in rheumatoid arthritis and Crohn's disease, would also be a logical choice for treating ENL and needs to be formally assessed in controlled studies.

Education of patients

Teaching leprosy patients about their disease is the key to successful management. The patient needs to be reassured that within a few days of the start of antibiotics he or she will not be infectious and can lead a normal social life. A clear explanation of the disease and refutation of myths about leprosy will help the patient come to terms with the diagnosis and might well improve adherence with treatment. The physician should emphasise that gross deformities are not the inevitable endpoint of disease, and that care and awareness of the limbs is as important as antibiotics. One advantage of supervised MDT is that the monthly visits permit continued education and surveillance for reactions.[86]

Prevention of disability

The morbidity and disability associated with leprosy are secondary to nerve damage. The patient's self-awareness is crucial so that damage is minimised. A patient with an anaesthetic hand or foot needs to understand the importance of daily self care, especially protection when undertaking potentially dangerous tasks, and inspection for trauma. Studies of self care show a reduction in hand and foot ulcers when patients are trained.[131] Anaesthetic feet need protective footwear, but special shoes are difficult to produce and can increase stigma. A randomised controlled trial of footwear for leprosy patients showed that cheap canvas shoes with cushioned insoles were protective, cost-effective, and preferred to orthopaedic shoes.[132] Plantar ulceration is secondary to increased pressure over bony prominences, exacerbated by loss of protective sensation or deformity. Ulcers should be treated with rest because, unlike ulcers in diabetic or ischaemic feet, ulcers in leprosy heal if they are protected from weight-bearing.[133] No weight-bearing should be permitted until the ulcer has healed. More complicated

ulcers require surgical management by removal of dead tissue with wide exploration and good drainage. Antibiotics should be used only for deep bony infection or septicaemia. Contractures of hands and feet, foot drop, lagophthalmos, entropion, and ectropion are amenable to reconstructive surgery.[134]

Socioeconomic rehabilitation

Recent assessments of socioeconomic rehabilitation have highlighted the importance of involvement of the client, the family, and the community in the rehabilitation process, and suggested that such involvement is best delivered through general community-based rehabilitation programmes.[135] IDEA (International Association for Integration, Dignity and Economic Advancement) has assisted in the development of community-based approaches to the integration and support of people previously affected by leprosy.[136]

Prophylaxis against leprosy

BCG gives variable protective efficacy against leprosy in different countries, ranging from 34% to 80%. In a trial in Malawi, BCG induced 50% protective efficacy against clinical leprosy, both tuberculoid and lepromatous forms,[137] and reimmunisation with BCG increased the protective effect by a further 50%. This protective effect of BCG has been confirmed in many case-control studies. Therefore, BCG immunisation of children for tuberculosis can also contribute to leprosy control. The addition of heat-killed *M leprae* to BCG did not increase the protective effect of BCG in two trials in Malawi and Venezuela[137,138] but did in a recent large study in India, resulting in a protective efficacy of 64%.[139] That study also showed significant protective efficacy (65%) with the cultivable mycobacterium, ICRC.[139]

In endemic countries, contact with leprosy patients is a risk factor for disease,[20] and chemoprophylaxis of close contacts of leprosy patients can be an effective control strategy.[21] A major prospective study of chemoprophylaxis with bactericidal drugs in contacts of leprosy patients is under way in Bangladesh to address this issue.[140] In non-endemic areas disease presenting in the contacts of leprosy patients is rare. The last case of secondary transmission in the UK was in 1923. Household contacts of new patients should be examined for clinical signs of leprosy and advised to report any new skin lesions promptly and to tell their physicians that they have had contact with a known case of leprosy. In the UK, BCG vaccination is given to household contacts under the age of 12 years. Close contacts of lepromatous cases under 12 years old are given prophylaxis with rifampicin 15 mg/kg once a month for 6 months.

Women and leprosy

Women with leprosy are in double jeopardy, because not only might they develop postpartum nerve damage, but also they are at particular risk of social ostracism with rejection by spouses and family.[141] There is little evidence that pregnancy itself causes new disease or relapse. There is, however, a clear temporal association between the development of type 1 reactions and neuritis and parturition, when cell-mediated immunity returns to prepregnancy intensity.[142] In an Ethiopian study, 42% of pregnancies in patients with borderline-lepromatous disease were complicated by a type 1 reaction during the postpartum period. In the same cohort, patients with lepromatous leprosy experienced ENL reactions throughout pregnancy and lactation. ENL in pregnancy is associated with earlier loss of nerve function than in non-pregnant individuals. Rifampicin, dapsone, and clofazimine are safe during pregnancy. Ideally, pregnancies should be planned when leprosy is well controlled.

What is necessary to eradicate leprosy?

The major commitment of national governments, WHO, non-governmental organisations, and international donor bodies has resulted in improved leprosy control and the large fall in leprosy prevalence observed over the past decade. However, the perception that leprosy has reached an arbitrary point at which it is no longer a public-health problem could lead to a reduction in control measures at the very time when further efforts are required. The continuing detection of new leprosy cases at an unchanged rate indicates that sustainable leprosy control programmes should be maintained so that the recent gains are not lost. What will be required to eradicate leprosy completely as a human disease? The cornerstone of any effective programme will remain MDT and early case detection based on passive case finding. Leprosy control activities are being integrated into general health services in many endemic countries, and this period of integration requires careful planning and implementation or the needs of leprosy control will be swamped by other pressing health problems, such as HIV/AIDS and tuberculosis. Elements of an effective programme will include the continuing provision of standard MDT drug packs through primary-health-care facilities, training of general health staff in leprosy diagnosis and treatment, the early treatment and referral of leprosy complications, the maintenance of expertise in leprosy in endemic countries, effective supervision and monitoring, and in some situations, special programmes for "difficult to reach" groups of patients. One positive outcome of MDT has been the wide recognition in leprosy-endemic communities that leprosy is curable. Appropriate community health education, that leprosy is treatable before disability occurs, is an important component of leprosy control to promote early presentation before the appearance of impairment of nerve function and disability. The development of tools to recognise infection with *M leprae* before the disease manifests itself might help to target prophylactic approaches. Finally, continued political commitment to leprosy control is essential, because these measures will be required for decades before leprosy can be judged a disease of the past.

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