Advances in the diagnosis and treatment of leprosy

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Leprosy is a chronic infectious disease caused by Mycobacterium leprae that mainly affects the skin and peripheral nerves. Over recent years, many important advances have been made in developing molecular diagnostics, in identifying highly effective drugs and designing multidrug regimens for treatment, and in unravelling the genomic structure and functions of the leprosy bacillus. Using the new information about specific sequences of M. leprae, several gene probes and gene amplification systems for confirming diagnosis and monitoring treatment have been developed. Among these, polymerase chain reaction (PCR)-based methods have been useful in confirming the diagnosis in paucibacillary leprosy (where few bacilli are present). RNA-targeting systems for monitoring the progress of treatment, in situ hybridisation techniques for analysing specimens with nonspecific histological features, and molecular methods for direct detection of rifampicin/dapsone resistance are other major technological advances with immense applied value. Several effective regimens for the treatment of leprosy have been developed, which include rifampicin, clofazimine and dapsone as core drugs. Although these regimens are generally satisfactory, limitations in terms of persisting activity and late reactions/relapses in paucibacillary leprosy, and persistence of dead and/or live organisms in multibacillary forms of the disease, have been observed.

The demonstration of the bacterial aetiology of leprosy in 1873 by the Norwegian Armauer Hansen (yielding the alternative names for leprosy of Hansen’s disease and Hanseniasis) is considered one of the important landmarks in the arena of infectious diseases. However, because it has not been possible to cultivate Mycobacterium leprae in vitro, progress in understanding the biology of leprosy bacillus has been very slow. The success achieved in growing leprosy bacillus in the mouse foot (Ref. 1) galvanised leprosy research, leading to extensive work in different animal models, development of new chemotherapeutic agents, and the analysis of the biochemical, antigenic and molecular structure of leprosy bacillus. These advances have culminated in important developments in terms of both molecular diagnostics for early diagnosis and effective regimens for the treatment of leprosy. This article briefly reviews the aetiopathology of
leprosy before focusing on recent advances in the diagnosis and treatment of leprosy.

**Aetiopathology of leprosy: an introduction**

*M. leprae*

*M. leprae*, a member of the family *Mycobacteriaceae*, is a straight or slightly curved rod-shaped organism, 1–8 µm long and 0.3 µm in diameter. It divides by binary fission, is Gram-positive, and strongly ‘acid fast’ following staining with basic fuchsin, which stains the bacteria pink. (In contrast, staining of *M. tuberculosis* is both acid fast and alcohol fast.) *M. leprae* is an obligate intracellular parasite, found predominantly in macrophages, where the organism commonly occurs in clumps or ‘globi’. The optimal growth of *M. leprae* is observed at 27–30 ºC, which is also reflected clinically, as the cooler areas of the body such as the skin, nasal mucosa, and superficial peripheral nerves (particularly Schwann cells) are the predominant sites of infection.

**Epidemiology**

The current geographical distribution of leprosy is shown in Figure 1. The global burden of the disease has decreased tremendously since the introduction of multidrug treatment (MDT) in 1982. Nearly half a million cases are estimated to remain worldwide, mainly in the Asian and African subcontinents (Table 1). Countries where leprosy continues to be a major problem include Brazil and India. Although no non-human sources of infection have been established, naturally occurring infection in monkeys and armadillos has been reported. *M. leprae*-like organisms have also been reported to be present in soil. The mode of transmission of leprosy has not been fully established, but nose and skin are considered as the main portals of exit as well as entry (Ref. 2).

**Clinical features and classification**

The incubation period of the disease is long and highly variable (usually 2–10 years). Most individuals exposed to infection are naturally infected before developing clinical symptoms.
protected, are able to mount an efficient immune response, and do not suffer from the disease. In those who suffer from the disease, the main clinical features in paucibacillary (PB) disease (see below) result from damage due to immune responses mounted by the host, whereas in the lepromatous (LL) forms bacillary load and to some extent immune response are responsible for the clinical presentation. Symptoms and signs pertaining to involvement of the skin and nerves are most commonly encountered, including hypopigmented macules and sensory loss (Ref. 3). At least two of the following findings have to be present for a clinical diagnosis of leprosy: (1) a characteristic patch or skin lesion with impaired sensations; (2) a thickened and/or tender cutaneous or peripheral nerve with impairment of sensations in the area supplied by it; and (3) acid-fast bacteria in the skin smear.

The disease is formally classified into a range of subtypes that include, in approximate order of extent of disease, ‘suspicious’, early indeterminate (I), tuberculoid (TT), borderline tuberculoid (BT), mid borderline (BB), borderline lepromatous (BL) and LL disease (Ref. 4). Other forms, such as pure neurotic leprosy (without skin lesions), are also recognised (Ref. 5). The degree and type of immune response and also probably the route of infection determine the clinical forms of the disease. Individuals with strong cell-mediated immunity (CMI) or delayed-type hypersensitivity (DTH) show a localised TT disease, whereas individuals lacking CMI progress from I to LL disease. The immune defect is specific to M. leprae; other immune responses remain intact. The disease is characterised by the formation of granulomas; these vary from epithelioid type in TT leprosy to foamy cell (macrophage) type in LL disease (Ref. 6).

The lepromin skin test, which measures DTH to M. leprae antigens, is used to assist diagnosis and classification of leprosy (Ref. 7). The response is biphasic, with an early response at 24–48 h, and a late response at 3–4 weeks. Bacterial load in the disease can be estimated from a smear, taken from skin lesions, stained for acid-fast bacteria. Density of bacteria (both viable and nonviable) is expressed using the logarithmic Ridley Scale [bacterial index (BI) 0–6] (Ref. 8). For treatment purposes, smear-positive BT, BB, BL and LL cases are referred to as multibacillary (MB) leprosy, whereas smear-negative I, TT and BT cases are termed PB leprosy (Ref. 9).

### Reactions and relapses

Episodes of acute inflammation in the leprosy lesions and/or in nerves and other body parts have been popularly referred to as ‘reactions’. It is hypothesised that these are brought about by disturbances in immunological balance as a result of immune reactivity to M. leprae antigens. Identical antigenic determinants of the host might also contribute to the autoimmune phenomenon. Three types of reactions are recognised. (1) Type I

### Table 1. Leprosy situation in 2000 by WHO regions (tab001vka)

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Cases on treatment</th>
<th>New cases reported</th>
<th>Cured with MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>64 490 (1.0)</td>
<td>55 635 (8.6)</td>
<td>645 576</td>
</tr>
<tr>
<td>Americas</td>
<td>90 447 (1.1)</td>
<td>45 599 (5.7)</td>
<td>256 670</td>
</tr>
<tr>
<td>South East Asia</td>
<td>574 924 (3.8)</td>
<td>621 620 (41.3)</td>
<td>9 507 660</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>8 785 (0.2)</td>
<td>5 757 (1.2)</td>
<td>72 463</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>13 771 (0.1)</td>
<td>9 501 (0.6)</td>
<td>273 161</td>
</tr>
<tr>
<td>Europe</td>
<td>846 (–)</td>
<td>172 (–)</td>
<td>3 683</td>
</tr>
<tr>
<td>Total</td>
<td>753 263 (1.25)</td>
<td>738 284 (12.3)</td>
<td>10 759 213</td>
</tr>
</tbody>
</table>

a Data from Ref. 98.
b Rate per 10 000 shown in parentheses.
c Rate per 100 000 shown in parentheses.
d All cases cured with MDT since its introduction (at different times in different regions).

Abbreviations: MDT, multidrug treatment; WHO, World Health Organization.
(reversal) reactions are associated with changes in CMI; BT, BB and BL patients usually suffer from these reactions, and if not promptly treated the reactions can result in nerve damage and deformities. (2) Type II reactions [erythema nodosum leprosum (ENL) reactions] affect patients with MB disease (BL and LL, and sometimes BB) and are thought to arise from deposition of immune complexes in target organs and skin. (3) The Lucio phenomenon, which is less well understood, is associated with extensive skin necrosis due to acute vasculitis and occlusion of arterioles whose endothelium is massively invaded by M. leprae. In addition to these classifications, episodes of inflammation or reactions occurring during treatment are known as ‘early reactions’, whereas when the same occur after stoppage of treatment they are known as ‘late reactions’. It is thought that late reactions are caused by dead bacteria or antigens.

Relapse in leprosy is defined as recrudescence of the disease activity after successful completion of a prescribed course of therapy. This is considered to result from multiplication of the few remaining live organisms. As there is an element of inflammation in the re-activation and appearance of new lesions, relapses are often confused with late reactions (presumed to be due to dead organisms). Clinically these two conditions overlap, and histology is also not always helpful in distinguishing the two. Currently available methods for determination of viability of M. leprae (including the mouse foot-pad assay, and bacillary ATP and substrate uptake assays) are reliable only in MB disease (Ref. 10).

Molecular techniques for diagnosis and monitoring of treatment for leprosy

Standard immunological and histological approaches for assessing leprosy have limited value for diagnosing new cases at the ‘suspicious’ and early I stages and for monitoring treatment. Immunological techniques for eliciting DTH and serological responses in leprosy are useful only for determining exposure, as the antigens and resultant response persist for a long time after subsidence of clinical or subclinical disease. Demonstration of acid-fast bacteria in skin smears is also often not sufficiently sensitive, and in histology assessment, some granuloma characteristics can suggest nonspecific dermatitis. Extensive information about the molecular structure and function of leprosy bacillus is now available (Ref. 11, 12, 13), and this has helped in developing molecular techniques for early diagnosis, monitoring of treatment and detection of drug resistance (Ref. 10, 14).

Molecular methods for diagnosis

Probes targeting stretches of DNA (Ref. 15) and ribosomal (r)RNA or rRNA genes of M. leprae (Ref. 16, 17, 18, 19) have been developed by various investigators. The probes targeting DNA need the presence of at least 10^4 copies of target DNA for a positive result (Ref. 15), whereas rRNA-targeting systems can be 10–100-fold more sensitive (Ref. 19); however, because of the small number of organisms present in specimens from PB cases, these probes serve only a limited purpose. During the past 10 years or so, several polymerase chain reaction (PCR) methods have been developed to amplify different gene stretches of M. leprae. These include the genes encoding various M. leprae proteins [18 kDa (Ref. 15), 36 kDa (Ref. 20), 65 kDa (Ref. 21, 22), leprosy serum reactive (LSR) (Ref. 23)] and rRNA (Refs 24, 25), and repetitive sequences (Ref. 26). These assays have been reported to be sensitive to 1–10 organisms and to be positive in 95–100% of BL/LL and 50–70% of TT, BL and I specimens (Refs 10, 14). rRNA-targeting probes have been developed into situ hybridisation protocols and have been found to be of value in confirmation of diagnosis in cases with nonspecific histological features (Mohan Natrajan, Central JALMA Institute for Leprosy, Agra, India, pers. commun.). Therefore, in situ hybridisation and immunohistological approaches (Ref. 27) provide good diagnostic strategies to enhance the sensitivity and specificity of histological diagnosis. Forty to fifty per cent of cases missed by standard histology can be confirmed by the use of molecular methods. Absence of positivity in the remaining cases could reflect the need to further optimise these methods, and/or the possibility that many cases with nonspecific histological features might not be leprosy. These probes and gene amplification assays can be of immense help for the diagnosis of early atypical PB leprosy and also in mass confirmation of diagnosis for epidemiological and research purposes (Refs 10, 14).

Molecular methods for monitoring treatment

As M. leprae has not been cultivated in any acceptable in vitro medium system, time-
Consuming and relatively insensitive animal models have to be used to assess *M. leprae* viability (Ref. 10). Molecular biology has provided an alternative effective technology route for this purpose.

When the PCR technology for detecting *M. leprae* gene sequences was introduced, it was reported that this might be useful both for diagnosis and for assessment of viable load, as a reduction in signals was found to correlate with loss of viability (Ref. 26). These trends were confirmed in subsequent studies (Ref. 28). However, because of the persistence of weak signals in some cases a long time after effective treatment (Refs 10, 29), DNA-based PCR assays appear to have limited application in monitoring treatment, particularly in distinguishing late reactions and relapses.

During recent years, molecular techniques for viability estimation of *M. leprae* have been developed that are based on a quantitative estimation of RNA levels by direct hybridisation with specific probes (Refs 10, 14, 30), or by amplification by PCR (Ref. 31) or isothermal reactions (Ref. 32). The method of grading the positivity levels of *M. leprae*-specific rRNA in the tissues has been useful for monitoring therapeutic responses (Ref. 30). Techniques such as reverse transcription (RT)–PCR targeting 16S rRNA (Refs 10, 31), and nucleic acid sequence-based amplification (NASBA) targeting 16S rRNA (Ref. 32), have been reported to be useful for the determination of viability of *M. leprae*. Cases with positive results indicate the presence of viable organisms and should be considered for antileprosy chemotherapy. Such approaches could also be helpful in differentiating conditions such as late reactions and relapses for patient care.

**Molecular methods for monitoring drug resistance**

The lack of a suitable in vitro cultivation system for *M. leprae* has also hindered assessment of drug resistance. Molecular biology has provided important tools to investigate the molecular mechanisms of drug susceptibility and resistance in leprosy. The use of dapsone and rifampicin as monotherapies to treat leprosy in the 1970s resulted in the rapid emergence of drug resistance. With the introduction of MDT the trend has been apparently reversed and at present drug resistance is not considered a major problem. However, as active surveillance studies have not been carried out, the exact magnitude of drug resistance currently is not known. As in *M. tuberculosis*, mutations in the *M. leprae rpoB* locus are associated with rifampicin resistance (Refs 33, 34). The basis of dapsone resistance appears complex, but mutations in the *M. leprae folP* locus have been found to be associated with a high degree of dapsone resistance (Ref. 35). PCR is used to directly amplify the target loci (*rpoB* for rifampicin and *folP* for dapsone) and mutations are confirmed by techniques such as hybridisation with appropriate probes or sequencing. Little is known about the basis of resistance for drugs such as clofazimine. With the use of new techniques for the detection of mutations directly from clinical specimens, surveillance programmes to determine the exact magnitude of drug-resistant mutants to rifampicin, and possibly other drugs, can be undertaken from the biopsies.

Sequencing of the genome of *M. leprae* has been completed (Ref. 36). The information generated opens new opportunities in functional genomics and proteomics. Such studies will undoubtedly provide scope to develop improved molecular methods for confirmation of diagnosis, for assessing prognosis and for detection of drug resistance.

**Current therapy for leprosy**

There have been rapid changes in the treatment of leprosy in the past few decades. The therapeutic scenario has moved from dapsone monotherapy in the 1970s to MDT using drugs such as dapsone, rifampicin and clofazimine. MDT was expected to shorten the length of treatment, leading to better patient compliance, and reduce the problem of drug resistance because of the combined use of multiple drugs with differing modes of action. MDT has indeed revolutionised the treatment of the disease and has been greatly welcomed by patients and doctors alike. More recently, several newer, more-potent drugs and immunomodulators have been introduced in the treatment of leprosy. This has increased the scope for further improvement in the treatment of the disease.

**Evolution and current status of WHO MDT regimens**

The World Health Organization (WHO) introduced MDT in 1982, and advocated short-course treatment regimens (Ref. 37). According to WHO guidelines, PB patients were to be treated...
with two drugs [rifampicin (600 mg, once a month, supervised) and dapsone (100 mg, daily, unsupervised, for 6 months)]. As most of these patients are lepromin-positive, it was thought that any residual organisms remaining after stoppage of therapy would be taken care of by the immunity of the host. Treatment for MB patients comprised three drugs [rifampicin (600 mg, once a month, supervised), clofazimine (300 mg, once a month, supervised; along with 50 mg, daily, unsupervised) and dapsone (100 mg, daily, unsupervised)]. The treatment was to be given for 2 years or until the attainment of smear negativity – whichever was earlier.

In the early 1990s, the concept of fixed-duration treatment (FDT) was introduced for control programmes. It was advocated that treatment in PB cases should be stopped after completion of six supervised doses taken in a maximum of 9 months, and treatment in MB cases be stopped after completion of 24 supervised doses in 36 months, irrespective of whether the smears were positive or negative (Ref. 38). This duration has been further reduced to 12 months for MB cases, and a single-dose regimen comprising rifampicin (600 mg), ofloxacin (400 mg) and minocycline (100 mg) (ROM) has been recommended for mono-lesion cases (Refs 39, 40). These regimens have already been implemented by control programmes in some countries, such as India (Ref. 41).

Although ROM and 12-month FDT regimens have been introduced only recently, considerable experience has accumulated on the application of various earlier recommended MDT regimens. The overall response has been good. With MDT, there is rapid killing of *M. leprae* and also faster negativity has been observed from the main portal of exit and dissemination – the nose. Confidence in the results has led to the declaration of ‘cured’ patients, and thus the prevalence of recorded leprosy cases has declined significantly worldwide. Problems of drug resistance using these regimens also appear to be under control. However, some limitations have been consistently observed, and in order to achieve more-effective patient care and control of the disease it is important to discuss these.

**Limitations in PB leprosy therapy**

On the whole, treatment in this group of patients appears satisfactory (Ref. 42). There are four issues that require debate, as follows.

First, residual disease activity in the lesions at the end of six months of treatment has been observed in the skin lesions in 10–67% of patients by various workers (Refs 42, 43, 44, 45, 46, 47). This persisting activity is lower in fresh leprosy cases reporting for treatment recently (Ref. 48). Follow-up studies have shown that this persisting activity does subside in some patients, but in others this worsens and requires further therapy (Refs 43, 44).

Second, there is the issue of late reactions. Late reactions usually occur after 6–18 months, but have also been reported up to 5 years after stoppage of therapy. After discontinuation of therapy, 5–21% of patients have been reported to suffer from late reactions (Refs 43, 45, 49). It needs to be emphasised that it is very difficult to distinguish reactions from relapses (Ref. 46). These conditions overlap not only clinically but also histologically. Using the mouse foot-pad assay (Ref. 50) and molecular probes targeting rRNA (Ref. 10), evidence for the presence of live organisms in specimens from cases clinically diagnosed as ‘late reaction’ has been reported. It is therefore at present too risky to treat these patients with steroids alone for long periods after stoppage of the MDT; additional MDT along with steroids would be more appropriate.

Third is the issue of relapse. The relapses can be defined as the gradual appearance of new lesions with increased reactivity in some or all old lesions, with or without nerve involvement or skin smear positivity. Relapse rates have varied from 0.1–1% in some studies (Ref. 47) to 6–13% in others (Refs 43, 44, 49). Some of this variation could be due to the different definition of relapses being used in different studies, and to the difficulty in the diagnosis because of the overlap between relapses and reactions. It has been observed that all the ongoing problems of persisting activity and reactions/relapses can be significantly reduced by extension of MDT (Ref. 45), additional dapsone therapy (Refs 43, 49), addition of clofazimine to the drug regimen (Ref. 48) and use of drugs such as prothionamide (Ref. 51). Of these, clofazimine appears to be the most attractive option, as the same regimen, with a different duration, can be administered to PB and MB patients. Experience with the use of other drugs such as minocycline in PB leprosy is very limited (Ref. 52). At present, these will perhaps be considered in cases with hypersensitivity and intolerability to conventional drugs.
Fourth, it is unclear how mono-lesion cases should be treated. After the widespread use of MDT, there has been a change in the profile of the disease, and a substantial proportion of fresh cases are presenting with single lesions as they are being diagnosed early. Such lesions are considered innocuous and capable of self healing. The 7th WHO Expert Committee (Ref. 39) has recommended a single dose of ROM for the treatment of these cases. These recommendations have been accepted by the national programmes in countries such as India (Ref. 41). In a study reported from India, nearly half of the cases treated with ROM and standard treatment with 6 months of PB MDT were inactive after 18 months of follow-up (Ref. 53). Promising results of ROM treatment in cases with two lesions have been subsequently reported (Ref. 54). These are at variance with earlier studies of responses in single-lesion cases from India (Ref. 55), and Malawi (Ref. 46). Such variance in observations indicates that it might be premature to conclude ROM is efficacious for single-lesion cases, which are likely to be heterogeneous and evolving cases. Published follow-up of these cases is inadequate (Ref. 56). Furthermore, there are several theoretical risks from the use of a single-dose treatment (Ref. 57). For example, some bacteria might not be multiplying at the time of administration of the drug and will therefore not be targeted; also, some cases will be MB or progressing towards MB disease, for which this single-dose regimen is absolutely inadequate.

Limitations in MB leprosy therapy

MB patients have a higher bacterial load and, to prevent the emergence of drug-resistant strains, treatment for 2 years or until smear negativity (Ref. 37) was recommended with at least three drugs: rifampicin, clofazimine and dapsone. This regimen has been found to be highly bactericidal and well tolerated, and is widely accepted. With this regimen, the incidence and severity of reactions decreased and the compliance of the patients has improved. Most of the MB patients become smear negative with 24 doses, although the highly bacillated cases require 5–6 years to become smear negative. Various modifications to the WHO regimen have been proposed. No additional benefits of an initial intensive course of rifampicin or monthly loading dose of clofazimine have been observed (Ref. 58). The response to the operationally easier FDT of 24 doses in 36 months has been good (Ref. 38). This regimen has been used worldwide during the past 5–6 years and overall relapses of less than 1% have been reported (Ref. 59).

Three important issues have emerged from these trials. First, even after 2 years of therapy, viable persisters have been reported in 9–16% of the initially highly bacillated (BI 3–6+) patients (Refs 60, 61). Relapse rates of 2.9% after a follow-up of 3–5 years, increasing to 20% after a follow-up of 7.5 years, have been recorded (Ref. 62). Such high relapse rates have also been reported by others (Ref. 63). Second, an important problem in FDT-treated cases is the occurrence of repeated reactions and therefore continuing morbidity after stoppage of treatment. These patients require treatment with steroids, which is given without the cover of MDT. Chemotherapy along with steroids is desirable as a section of these cases are known to harbour live bacilli. Third, on the basis of theoretical considerations and limited published work (Refs 40, 64), the WHO and some programmes have recommended stoppage of treatment in MB patients after 12 doses (over 1 year) using the standard WHO regimen. It has been reported that rates of decline in BI in leprosy in cases treated for 12 months or 24 months were similar (Ref. 64). However, in another study, high relapse rates in patients with high BI defaulting after 12–16 months of therapy have been reported (Ref. 65). Considering the problems of persisters/relapses even with the 24-month regimen (Refs 62, 63), caution is required with the 12-month duration regimen. Intensive surveillance at least in selected areas for a period of 8–10 years is required for detection of relapses.

Treatment of MB leprosy with newer or alternative drugs

Several newer drugs active against M. leprae have emerged that are being evaluated to improve the treatment and reduce the duration of treatment in MB leprosy. Prominent among these are: quinolones (pefloxacin, ofloxacin and sparfloxacin, moxifloxacin); ansamycins (rifabutin, KRM-1648); macrolides (clarithromycin); tetracyclines (minocycline), fuscidic acid and other sulphones (brodimoprim). Of these, quinolones, minocycline and clarithromycin appear to be the front runners in providing alternative drug treatment for MB leprosy (Refs 66, 67). However, experience of clinical application and the establishment of appropriate regimens of...
these newer drugs are limited. Trials have been conducted in MB patients with an intensive short-course regimen consisting of daily treatment with 600 mg rifampicin plus 400 mg of ofloxacin for 1 month. The treatment was then stopped and patients followed-up on placebo (Refs 64, 68). The initial results suggest that the regimen is well tolerated, but high relapse rates have been observed (Refs 68, 69). Trials have also been conducted using the addition of supervised monthly doses of 100 mg minocycline plus 400 mg ofloxacin to the standard MB MDT regimen, with the treatment stopped after 1 year (Ref. 70). The response to the therapy was satisfactory during the treatment and early follow-up period (Ref. 70); however, conclusions can be drawn only after a longer and adequate follow-up.

Role of immunotherapy in the treatment of leprosy
Besides the presence of a small population of viable organisms (‘persisters’) after therapy, the problem of persistence of a large pool of dead bacilli is often encountered. Immunomodulators that can stimulate CMI have been applied to reduce this pool. These agents can be divided into three broad groups: drugs, antigenically related mycobacteria, and other immunomodulators (Ref. 71).

In the drug category, levamisole (Ref. 72) and zinc (Ref. 73), when used as an adjunct to dapsone therapy, have been reported to be useful, as seen by clinical improvement in the lesions and a decrease in the incidence and severity of reactions. Although both are considered to be immunopotentiators of CMI, their exact mechanisms of action are not completely understood. Furthermore, these compounds have not been adequately investigated along with MDT.

Antigens of various mycobacteria have been observed to cross-sensitise the immune response to M. leprae and this might help in augmenting CMI in leprosy (Ref. 71). Prominent among these are Bacille-Calmette Guerin (BCG) (Ref. 74), BCG plus killed M. leprae (Ref. 75), Mycobacterium w (Mw) (Refs 74, 76, 77, 78, 79, 80), and Indian Cancer Research Centre (ICRC) bacillus (Ref. 81). BCG, when administered to patients once in 6 monthly repeated injections along with MDT, resulted in a faster killing of bacilli, a more rapid fall in BI, a reduced incidence of reactions and a faster attainment of smear negativity as compared with the control group, who received placebo with the same MDT (Ref. 74). The combination of BCG plus killed M. leprae has been reported to have an immunomodulatory role in I and LL patients, and in lepromin-negative contacts of leprosy patients (Ref. 75). Mw, a cultivable mycobacteria that has antigenic similarities with M. leprae, has been investigated in different trials in humans and has been found to be safe and well tolerated. Compared with MDT, MDT plus Mw has been observed to enhance bacterial killing (Ref. 74), clearance of bacilli (Refs 74, 76, 80) and clearance of granuloma (Refs 78, 79, 80). As the granuloma and bacilli are cleared faster, a reduced severity and frequency of reactions has been observed (Ref. 77). Combined chemotherapy and immunotherapy with ICRC has been shown to significantly accelerate bacterial clearance (Ref. 81). M. vaccae also shares some antigens with M. leprae and has been proposed as an immunotherapeutic agent (Ref. 82).

Several other mediators of immune responses, such as transfer factor (Ref. 83) and various cytokines such as recombinant interferon γ (IFN-γ) (Refs 84, 85, 86, 87) and interleukin 2 (IL-2) (Ref. 88) have been used to treat leprosy. Transfer factor induced transient effects such as lepromin conversion (from negative to positive), granuloma formation and increased influx of lymphocytes locally (Ref. 83). Intralesional administration of IFN-γ in leprosy patients induced accumulation of lymphocytes and monocytes at the local site of injection (Refs 84, 85, 86). There was a distinct fall in the BI at the local site, with formation of epithelioid granuloma and occurrence of a reversal reaction in some cases, and enhanced bacterial clearance with IFN-γ has also been reported. However, repeated doses of IFN-γ have to be given intralesionally to induce systemic effects and have been associated with ENL reactions in LL patients (Ref. 87). The administration of IL-2 also accelerated bacterial clearance (Ref. 88); however, these effects were seen only at the local site.

Therapy of reactions
Efficient management of reactions to prevent nerve damage requires good clinical judgment in making an appropriate early diagnosis and assessing the extent of severity in terms of nerve deficit and multi-organ involvement. The treatment of reactions is based on suppression of inflammation and its consequences. The
frequency and severity of ENL reactions in BL/LL cases have been greatly reduced by administration of clofazimine. Many drugs, such as salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), chloroquin, antimonials, steroids, pentoxyphlline, thalidomide and others, are used in the management of ENL (Refs 89, 90). Steroids continue to provide the mainstay of management of type I reactions in borderline and tuberculoid patients. Standard steroid regimens have been described to control reactions (Ref. 89); however, the standard WHO regimen is considered too short (Ref. 90). The efficacy of drugs such as cyclosporin has been reported to vary from modest to highly effective for the treatment of type I reactions (Ref. 90). The application of molecular tools for quantitative estimation of cytokines by mRNA-based methods and quantitative PCR (Refs 91, 92), is leading to a better understanding of mechanisms and also of the effects of treatment. Earlier compartmentalised concepts of type 1 and type 2 immunity in tuberculoid versus lepromatous cases, respectively, and immune complexes as solely responsible for ENL and DTH for reversal reactions, are now changing with the new evidence. These studies have shown upregulation of T helper 1 (Th1) responses in ENL (Refs 91, 92).

A subgroup of patients showing a slower response to steroids that correlates with cytokine profiles (Ref. 92) needs to be followed up to identify patient groups and markers that might help in deciding upon appropriate treatment. Steroid dependence is a serious problem and thalidomide analogues might provide a possible option, although these are still under development (Ref. 93).

**Future challenges**

The treatment of leprosy has improved significantly over recent years and this has helped to tackle the disease at the public health level. However, optimal regimens are still evolving. Some of the recently recommended regimens such as single-dose ROM and 12-month FDT need to be kept under close scrutiny for some time, and various modified regimens that have shown promising results need to be considered for improving the therapy. The idea of developing a common regimen for PB and MB leprosy is also gaining momentum (Refs 42, 48, 67) and needs to be pursued. The addition of newer effective drugs such as ofloxacin and minocycline to treatment regimens is increasing, and their potential in effectively reducing the duration of treatment and the management of special situations such as resistance or intolerance is apparent. Many patients require individual attention and tailor-made treatment. Indications for such improvisations could be a poor response to standard treatment and hypersensitivity to some of the drugs. For such patients, replacement of the drug(s) might be required (Refs 94, 95). Currently, several WHO- and ILEP-sponsored trials to monitor various regimens, including some new alternatives, are progressing (Ref. 95).

As the total patient load has been considerably reduced, easy diagnostic methods such as skin smears for acid-fast bacilli should be re-introduced for monitoring of cases at field-level clinics. Molecular methods should be available at reference laboratories and be more extensively used in research and epidemiological studies.

Leprosy has been a feared disease mainly because of the deformities associated with it. After widespread use of MDT, there has been a sea change in the profile of the disease. Early and appropriate treatment undoubtedly helps in reducing the severity and frequency of deformities. Nevertheless, disabilities continue to be a major problem (Ref. 96). Different preventive (management of reactions, nerve decompression) and corrective (tendon transfers, management of plantar ulcers) procedures to manage deformities are available. Besides the availability of surgery, timely physiotherapy and health education are very important in the prevention, management and rehabilitation resulting from the disabilities. As leprosy patients continue to have disabilities for a long time or even life, these services will be required for a much longer time.

Genuine concerns have been raised about the continued high-incidence rates of leprosy even in areas with intensive MDT campaigns for 10–15 years. The issues of inadequate coverage, non-human sources, extraordinarily long incubation periods and effectiveness of regimens being used need to be analysed for these unexpected results. The rich experience of the past of treating leprosy patients with different regimens, together with lessons from careful follow-up of new regimens and the appropriate use of molecular tools for early diagnosis and surveillance of drug resistance, provide an excellent base from which to progress towards the goals of sensitive and specific diagnostics as well as optimal regimens.
for all leprosy patients. The knowledge emanating from analysis of the human genome and the *M. leprae* and *M. tuberculosis* genomes (Ref. 97) will undoubtedly strengthen the development of relevant technologies for more-effective management of leprosy at patient and public health levels.

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References
16 Katoch, V.M. et al. (1994) Progress in developing ribosomal RNA and rRNA gene (s) based probes for the diagnosis and epidemiology of infectious diseases including leprosy. In Tropical Diseases – Molecular Biology and Control Strategies (Kumar, S., ed.), pp. 581-587, Council of Scientific and Industrial Research, New Delhi, India
22 Hackel, C. et al. (1990) Specific identification of...


41 Directorate General (Leprosy Division), Nirman Bhawan (1997) Modified guidelines on MDT regimen to be followed under NLEP. L. 19025/6/97, Government of India, New Delhi


45 Bhate, R.D. et al. (1986) Experience with multidrug therapy in paucibacillary leprosy. Indian J Lepr 58, 244-250, PubMed ID: 87110928


47 Bexx-Bleumink, M. (1992) Relapses in leprosy patients after release from dapsone monotherapy; experience in the leprosy control
program of the all Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. Int J Lepr Other Mycobact Dis 60, 161-172, PubMed ID: 92395341


51 Katoch, K. et al. (1992) Treatment of paucibacillary leprosy with a regimen containing rifampicin, dapson, and prothionamide. Indian J Lepr 64, 303-312, PubMed ID: 93056787


54 (2001) A comparative trial of single dose chemotherapy in paucibacillary leprosy patients with two to three skin lesions. Indian J Lepr 73, 131-143, PubMed ID: 21464104


60 Subcommittee on clinical trials of scientific working group on chemotherapy of leprosy (THELEP) of UNDP/ World Bank/WHO special programme for research in tropical diseases (1987) THELEP controlled clinical drug trials. Int J Lepr 55 (Suppl. 4), 864-868


64 Ganapati, R. et al. (1997) Rate of decline in bacterial index in leprosy; observations after three different chemotherapeutic interventions. Int J Lepr Other Mycobact Dis 65, 264-266, PubMed ID: 97395466


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https://doi.org/10.1017/S1462399402004763
77 Kar, H.K. et al. (1993) Reversal reaction in multibacillary leprosy patients following MDT with and without immunotherapy with a candidate for an antileprosy vaccine, Mycobacterium w. Lepr Rev 64, 219-226, PubMed ID: 94048880
Further reading, resources and contacts

The WHO's Action Programme for the Elimination of Leprosy provides current information on therapy, endemic countries, research and publications.

http://www.who.int/lep/

LEPRA is a UK-based medical development charity whose prime objective is to eradicate leprosy.

http://www.lepra.org.uk/

The Novartis Foundation for Sustainable Development 'has been actively involved in leprosy programs in Asia, Africa and Latin America in partnership with local health authorities, the WHO and non-governmental agencies'. The efforts of the foundation focus primarily on eliminating leprosy, and their website is a useful source of information on the diagnosis, treatment and elimination of the disease.

http://www.novartisfoundation.com/leprosy/index.htm

Leproma is a powerful web-based tool for extracting information on gene structure and function from a Mycobacterium leprae genome database, using programmes such as BLAST and FASTA.

http://genolist.pasteur.fr/Leproma

Features associated with this article

Figure
Figure 1. Global leprosy situation in 2000 (fig001vka).

Table
Table 1. Leprosy situation in 2000 by WHO regions (tab001vka).

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