Update on Leprosy in Immigrants in the United States: Status in the Year 2000

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The World Health Organization established a goal in 1991 of “elimination of leprosy as a public health problem by the year 2000.” Although prevalence rates of leprosy have decreased in many geographic areas, it is clear that in some countries where leprosy is endemic, such as Brazil and India, this goal will not be reached. Leprosy is rare in the United States, but 85% of detected cases are in immigrants in whom the disease may mimic many common dermatologic and neurological entities, leading to delay of diagnosis. The statuses of polymerase chain reaction analysis, serological testing, and vaccines are reviewed. Effective multidrug therapy and prevention of permanent damage to nerves by early recognition and treatment will help prevent residual disabilities. This update reviews what is known about the pathophysiology and treatment of leprosy. Increased awareness will lead to earlier recognition, diagnosis, and treatment.

In May 1991, the World Health Organization (WHO) adopted a resolution establishing a goal of “elimination of leprosy as a public health problem by the year 2000” [1]. Elimination was defined as a prevalence of ≤1 case per 10,000 population, with a case being defined as leprosy in a patient who received or required chemotherapy. Implementation of a short course of multidrug therapy [2] worldwide since 1982 had resulted in many patients completing treatment and being removed from global case registers. Significant declines in incidence had also occurred in some countries, such as China and Mexico, before the introduction of multidrug therapy. This decline was thought to be secondary to better nutrition and living conditions [3], although widespread BCG vaccination, which has been shown to be effective against leprosy in Africa [4], may have played a role in certain areas. This new WHO case definition helped to revise their estimates of total cases downward from 10–12 million to ~5.2 million worldwide in 1991 [2]. The idea of reducing the prevalence to ≤1 case per 10,000 population assumes that the reservoir of infection and therefore the potential for transmission will eventually be eliminated.

Multidrug therapy, however, has not been shown to decrease the transmission or case detection rate in countries in which full multidrug therapy coverage has occurred. Therefore, some authorities continue to question the success of the goal of the control program in terms of prevalence rather than incidence. It is clear, at this point, that in some countries where leprosy is endemic, such as India and Brazil, the elimination strategy of the WHO will not reach its goal by the end of the year 2000 (The year set forth by the WHO for the goal for the elimination of leprosy has therefore been pushed backward to 2005). These prevalence numbers of the WHO also do not take into account patients who may have significant residual disabilities after multidrug therapy and require ongoing treatment or rehabilitation.

EPIDEMIOLOGY

Leprosy is rare in the United States. The total number of newly registered cases (both treated and untreated) in the National Hansen’s Disease Program was 102 in 1998 (unpublished data, National Hansen’s Disease Program). There has been a trend toward decrease since 1991, when there were 297 new cases; 85% of detected cases in the United States are in immigrants (unpublished data, National Hansen’s Disease Program). Small numbers of endemic cases are reported from Texas, Hawaii, and Louisiana. An increase in imported cases to the United States was identified from 1978 through 1988 by reviewing surveillance data from the Centers for Disease Control and Prevention [5]. This increase was primarily among the large
groups of refugees from Laos, Vietnam, and Cambodia. The diagnosis of leprosy was usually made during the first year after entry into the United States. Most of the imported cases were lepromatous leprosy or borderline leprosy, but there was no evidence that the imported cases resulted in transmission in the United States.

Although approximately 70% of the estimated number of cases of leprosy in the world are still in patients from Southeast Asia, most of the newly diagnosed patients in our clinic in the last 10 years have originated from Latin America, especially Brazil. Physicians who take care of migrant or refugee populations are, therefore, more likely to encounter this disease in their practices.

**DIAGNOSIS**

Leprosy can superficially mimic many dermatologic and neurological entities (table 1). Anesthetic skin or mucous membrane lesions in the presence of thickened nerves are the hallmarks of leprosy. Detection of acid-fast bacilli in slit-skin smears or skin biopsy specimens, which should include subepidermal tissue, confirms the diagnosis. Patients are classified by the WHO [6] as having paucibacillary disease when no bacilli are demonstrated and multibacillary disease when bacilli are seen on slit-skin smears. Acid-fast staining by Fite’s method [7] of skin biopsy specimens is preferable for the detection of *Mycobacterium leprae*, as these organisms may be decolorized with Ziehl-Neelsen stain. The density of bacilli is recorded logarithmically as the bacterial index.

Antibodies to species-specific lipid antigens of *M. leprae*, such as phenolic glycolipid 1, are not sensitive enough to use for diagnosis of the individual patient, although there is a high rate of seropositivity among patients with multibacillary disease when studied in native populations with leprosy [8]. Most patients with paucibacillary disease do not have a detectable humoral response. Furthermore, follow-up studies have shown that newly diagnosed leprosy can be found in the contacts of seronegative index patients [9].

In regions where the prevalence of leprosy is low, other methods of diagnosis, such as PCR analysis, have been found to yield positive results only when biopsy specimens that had detectable organisms by Fite’s method were tested [10]. As such, PCR analysis is only useful clinically to support a diagnosis of leprosy if atypical clinical or histological features are present.

**PATHOGENESIS**

The etiologic agent, *M. leprae*, is an obligate intracellular parasite that has a generation time of 12.5 days. *M. leprae* grows best at 27°C–30°C in the experimental mouse footpad model [11] and in humans, but it has not been cultured in vitro.

<table>
<thead>
<tr>
<th>Type of lesion, ailment</th>
<th>Differential diagnosis of leprosy: types of lesions that leprosy superficially mimics.</th>
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<tbody>
<tr>
<td>Hypopigmented macular lesion</td>
<td>Naevus anemicus</td>
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</table>
| Hy...
Although humans are considered the major host and reservoir, leprosy has been found in armadillos and primates [12]. The armadillo has become the main source of *M. leprae* for laboratory studies and the preparation of vaccines. In Texas and Louisiana, up to one-half of the wild armadillos have naturally acquired leprosy.

The mode of transmission of leprosy is not well understood: household contacts of patients with borderline leprosy and lepromatous leprosy whose nasal mucosae are heavily infected with bacilli are at much higher risk of acquiring the disease. Transmission may occur primarily by sneeze aerosols and direct contact with ulcerated skin lesions. The presence of phenolic glycolipid 1 in soil [13] also suggests possible transmission of this mainly rural disease through contaminated soil.

The large variation of the host response to infection with *M. leprae* has been demonstrated to be influenced by genetics. Familial clustering is well documented, and concordance rates among identical twins are high [14]. Susceptibility to leprosy is linked to the NRAMP1 gene, which in mice controls innate susceptibility to mycobacterial infections [15]. HLA genes influence the type of leprosy that develops during infection [16]. For example, tuberculoid leprosy develops more frequently in individuals with HLA-DR3, whereas lepromatous leprosy is more prone to develop in those with HLA-DQ1 or HLA-MT1.

Immunodeficiency associated with HIV type 1 infection has not affected the case detection rate or the outcome of treatment for patients with leprosy [17, 18]. However, pregnancy, which causes a relative decrease in cellular immunity, may precipitate new reactions or relapses in patients with leprosy [19].

**CLINICAL FEATURES**

The incubation period of leprosy ranges from 3 months to 40 years (average range, 2–4 years). The onset of leprosy is insidious. The skin and peripheral nervous system are primarily involved. The expression of disease caused by *M. leprae* results from the interaction between the organism and the immune system of the infected host. Most infected individuals have effective immunity without disease, whereas other persons have a spectrum of clinical manifestations (figure 1) at presentation that correlates with the cell-mediated immune response of the patient (classification of Ridley and Jopling [20]). This spectrum includes indeterminate leprosy, tuberculoid leprosy, borderline tuberculoid leprosy (figure 2), borderline leprosy, borderline lepromatous leprosy (figure 3), and lepromatous leprosy.

At one end of the spectrum of clinical manifestations of leprosy, patients with tuberculoid leprosy exhibit relatively good cell-mediated immunity against *M. leprae*. Some patients who have less effective cell-mediated immunity against *M. leprae* have a more aggressive clinical and bacteriologic expression of the disease, known as “borderline leprosy.” Finally, some patients are anergic to *M. leprae*, and widespread systemic disease develops that involves not only the skin and upper respiratory tract but also the anterior chamber of the eye, the testes, the lymph nodes, the periosteum, and the superficial sensory and motor nerves. A difference in cytokine responses has also been demonstrated in tuberculoid leprosy versus lepromatous leprosy, with primarily a Th1 profile being expressed in tissue specimens from patients with tuberculoid leprosy and borderline tuberculoid leprosy and the predominance of mRNA from Th2 cytokines being found in tissue specimens from patients with lepromatous leprosy.

The bacilli favor the cooler areas of the body, such as the chin and malar areas of the face, earlobes, buttocks, knees, and distal extremities. Skin lesions range from the asymptomatic, ill-defined, slightly hypopigmented macule of indeterminate leprosy, to diffuse infiltration of the skin seen in lepromatous leprosy that causes thickening of the skin of the face and earlobes and produces classic leonine facies. Eyebrows and eyelashes can be lost (madarosis), and anesthesia of affected areas is extensive and accompanied by anhidrosis in lepromatous leprosy.

Leprosy reactions are acute inflammatory syndromes, which...
punctuate the course of chronic infection with *M. leprae*. They continue to be important causes of disability, despite successful chemotherapy, and occur in up to one-third of patients. They can be divided into 2 types: type I, upgrading or reversal reactions and downgrading reactions; type II, erythema nodosum leprosum (ENL) (table 2). Downgrading reactions were described in untreated patients and are not frequently encountered now. TNF-α, which is overproduced, is a key mediator of systemic symptoms and tissue damage during both reversal reactions and ENL [21]. Expression of mRNA from TNF-α is also elevated in patients with these reactions, especially patients with active neuritis. It is hypothesized that a high antigen load released by dying mycobacteria leads to immune complex formation, which in turn will cause TNF-α secretion from macrophages; this secretion will lead to the vasculitis seen in ENL.

Elevated serum levels of IFN-γ have also been found in patients with ENL. The IFN-γ level correlates with the intensity of the inflammatory state. In patients with multibacillary leprosy, intradermal injections of recombinant IFN-γ induced ENL [22]. ENL can also be triggered by vaccination, tuberculin skin tests [23], or other immune stimulation. In addition, autoantibodies to SS-B, and cardiolipin are frequently found in patients with lepromatous leprosy [24]. The antiphospholipid antibody syndrome, characterized by necrosis of skin and gangrenous digital changes that result from the hypercoagulable state, may develop in some patients [25]. This syndrome may mimic Lucio’s phenomenon, in which patients with lepromatous leprosy and heavy bacterial loads develop vasculitis and slowly healing ulcers in the lower extremities (which are often secondarily infected).

Both reversal reactions and ENL can occur before, during, and after multidrug therapy. A decline in ENL has been observed since the introduction of multidrug therapy and is attributed to the anti-inflammatory effects of daily clofazimine treatment (see section below, “Drug Treatment”). Recurrences of both reversal reactions and ENL are common, especially the latter (45% of patients), often necessitating prolonged use of steroids [26] (table 2). Long-term maintenance therapy with thalidomide may be necessary to prevent constitutional symptoms and cutaneous lesions of ENL. Unfortunately, thalidomide does not help appreciably in the treatment of peripheral neuritis, iritis, and orchitis associated with ENL. Peripheral neuropathy induced by thalidomide is rare (<1%) in patients with ENL and may be difficult to detect clinically. It is usually reversible when treatment is discontinued.

Even with chemotherapy, nerve lesions, which are often progressive and irreversible, may develop in one-third of patients with leprosy, and prevention of permanent nerve damage is extremely important in the management of patients with leprosy. Because no standard system for grading nerve damage has

<table>
<thead>
<tr>
<th>Classification</th>
<th>Tuberculoid</th>
<th>Borderline Tuberculoid</th>
<th>Borderline Lepromatous</th>
<th>Lepromatous</th>
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<tbody>
<tr>
<td>WHO</td>
<td>Paucibacillary</td>
<td>Multibacillary</td>
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<tr>
<th>Variable</th>
<th>Type I: reversal reactions</th>
<th>Type II: erythema nodosum leprosum</th>
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<tr>
<td>Clinical features</td>
<td>Occurs in BT and BB but most common in BL. Skin lesions: new or increased inflammation in preexisting lesions. With or without acute inflammation of nerve trunks</td>
<td>Occurs in BL and LL. Skin lesions: groups of new small, tender erythematous subcutaneous nodules. Fever, arthralgia, neuritis, vasculitis, adenopathy, iridocyclitis, orchitis, and dactylitis</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Recent pregnancy, facial plaques, extensive skin involvement, and preexisting neuritis</td>
<td>Pregnancy, age &lt;40 y</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Increase in cell-mediated immunity to bacilli in dermis and Schwann cells leading to inflammation of skin and nerve trunks</td>
<td>Systemic inflammatory response to deposition of extravascular immune complexes formed from <em>Mycobacterium leprae</em> antigen</td>
</tr>
<tr>
<td>Management</td>
<td>Prolonged anti-inflammatory therapy, analgesia, and physical support of active neuritis. High doses of steroids (1 mg/kg) for 4–6 mo. Azathioprine and cyclosporines are also effective. Surgical decompression of swollen nerves if medical therapy has not been successful</td>
<td>Thalidomide is drug of choice. Systemic symptoms and pain alleviate in 24–48 h, and nodules in involute in 3 d. Starting dose (200 mg) may be decreased with control of symptoms. Pentoxifylline and colchicine may be effective in mild cases. Neuritis requires use of systemic steroids</td>
</tr>
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</table>

NOTE. BB, borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, lepromatous leprosy.
Table 3. Multidrug therapy regimens for leprosy that are recommended by the World Health Organization.

<table>
<thead>
<tr>
<th>Type of leprosy</th>
<th>Multidrug therapy regimen</th>
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<tr>
<td>Paucibacillary</td>
<td>Dapsone (100 mg daily) unsupervised plus rifampin (600 mg once monthly) supervised for 6 mo</td>
</tr>
<tr>
<td>Paucibacillary, single lesion</td>
<td>Rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) once monthly</td>
</tr>
<tr>
<td>Multibacillary</td>
<td>Dapsone (100 mg daily) plus clofazimine (50 mg daily) unsupervised with rifampin (600 mg once monthly) and clofazimine (300 mg once monthly) supervised for 12 mo. Rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) once monthly for 24 doses for patients who cannot take clofazimine. Clofazimine (50 mg daily) plus ofloxacin (400 mg daily) and minocycline (100 mg daily) for 6 mo followed by 18 mo of clofazimine plus ofloxacin or minocycline for patients who cannot take rifampin.</td>
</tr>
</tbody>
</table>

NOTE. Data are from [31].

been adopted, the accuracy of data available from long-term studies may be open to question. Nerve damage occurs secondarily to the disease process and during reactions. Intraneurial infection with M. leprae organisms has been found in all forms of leprosy, primarily in the cytoplasm of Schwann cells and in macrophages and endothelial cells within the nerve. The recent identification of the role of α-dystroglycan as the laminin α2-G receptor on the Schwann cell for M. leprae [27] represents an important step in understanding the neurotropism of this organism. TNF-α may also contribute to nerve damage in leprosy [28].

Patients with borderline lepromatous leprosy have the most extensive involvement of large nerves, and their predisposition to reactions puts them at risk for the most severe nerve damage. Damage to nerves results in anesthesia, impaired sweating, dryness, and muscle paralysis. The lack of sensation and the dryness of the skin increase the risk of injuries, with complicating infections producing osteomyelitis and ulcerations of digits. Because early steroid treatment of neural involvement has been demonstrated to decrease disability, all newly diagnosed patients should be warned of the signs and symptoms of neuritis during therapy and the importance of prompt steroid treatment. An inflamed facial patch near the eye is associated with a high risk for the development of facial nerve damage, and consequently prophylactic steroid therapy is recommended.

In some instances, despite adequate chemotherapy, asymptomatic nerve damage progresses insidiously for prolonged periods (“silent” neuritis) without other features of typical reversal reactions. Although cell-mediated inflammation is probably the major etiologic factor, Schwann cell dysfunction and postinflammatory fibrosis may also contribute to this silent neuropathy. If loss of function has not exceeded 3 months, it may improve with systemic steroid treatment.

DRUG TREATMENT

Until 1980, the treatment of patients with leprosy consisted of dapsone monotherapy. Multidrug therapy was recommended by the WHO in 1982 because of increasing resistance to dapsone [29]. Patients with leprosy were classified as having paucibacillary disease and multibacillary disease on the basis of findings of slit-skin smears. In the field and when no laboratory facilities are available, a clinical classification is used: patients with 2–5 lesions (combination of skin lesions and palpable nerves) are described as having paucibacillary disease, and those with >5 lesions are described as having multibacillary disease.

Rifampin, dapsone, and clofazimine were initially selected for multidrug therapy on the basis of results of mouse footpad experiments [30]. Rifampin is by far the most effective bactericidal drug against M. leprae, and a single dose kills 99.99% of organisms, rendering patients with lepromatous leprosy noninfectious within 2 days. It inhibits the β subunit of RNA polymerase of M. leprae and has an MIC of 0.3 μg/mL. The standard dosage of rifampin (600 mg monthly) in multidrug therapy regimens has proved to be relatively nontoxic, although rare instances of renal failure, thrombocytopenia, hemolytic anemia, and hepatitis have been reported.

Dapsone is a slow-acting bacteriostatic drug with a short half-life; it competitively inhibits p-aminobenzoic acid and interferes with metabolism of folate. Resistance to dapsone, which can be primary or secondary, had reached very high rates by the 1970s, approaching 40% in some countries. Side effects include mild hemolysis (severe if the patient is glucose-6-phosphate dehydrogenase–deficient), allergic rashes, methemoglobinemia, and agranulocytosis.

The activity of clofazimine is equal to that of dapsone, but it has additional anti-inflammatory activity. Clofazimine commonly causes skin pigmentation and concentrates in areas with
high bacterial loads. It accumulates in Peyer’s patches of small bowel mucosa and mesenteric lymph nodes and may cause a pseudolymphoma syndrome. Gastrointestinal side effects are common, and small bowel obstruction has been described in association with high doses.

Patients with paucibacillary disease are treated with rifampin and dapsone for 6 months (table 3). Patients with multibacillary disease are treated with rifampin, dapsone, and clofazimine for 2 years. Since 1982, relapse rates have been considered low enough for the WHO to recommend further decreasing the duration of therapy for patients with multibacillary disease to 1 year in worldwide control programs [31]. The recommendations of American authorities on leprosy differ from the WHO regimens in that rifampin is administered daily and the length of treatment and follow-up is longer because of concerns about relapses (table 4).

Oflloxacin, minocycline, and clarithromycin also display modest bactericidal effects, but these effects are much less than those of rifampin. All 3 drugs are usually absorbed well and are associated with few significant side effects. In an effort to shorten and/or simplify therapy, 3 bactericidal agents (rifampin, ofloxacin, and minocycline) in single doses are now being used in combination in clinical trials for treatment of single-lesion paucibacillary disease. Although the combination of rifampin, ofloxacin, and minocycline has been shown to be associated with success rates similar to those associated with rifampin and dapsone for 6 months as treatment of single-lesion paucibacillary leprosy, long-term relapse rates have not yet been reported. Other ongoing trials include this combination monthly for 3–6 months for treatment of paucibacillary disease and 12–24 months for treatment of multibacillary disease.

The annual rate of relapse after multidrug therapy is stopped ranges from 0.01% to 0.14%. Relapses generally occur late, in at least 5 (±2) years. Reversal reactions can also occur during the first year after multidrug therapy is discontinued at a rate of 4.8%–9.0% [33]. Patients should therefore be checked every 3 months after discontinuing multidrug therapy to detect late reactions or relapses. It may be difficult to clinically distinguish relapses from reversal reactions after multidrug therapy, especially in paucibacillary disease, unless the results of skin smears have become positive. It has therefore been suggested that patients with these difficult cases should be given a 4-week trial of steroid therapy, since only those with reversal reactions will respond relatively rapidly to corticosteroid treatment (table 2).

Despite multidrug therapy, persisters (viable, physiologically dormant bacilli that remain fully drug susceptible and survive for many years despite the presence of bactericidal levels of drugs) have been observed in both paucibacillary disease and multibacillary disease [34]. The eyes and peripheral nerves may be common locations of persisters. Rifampin has little effect on dormant bacillary populations, and the addition of dapsone and clofazimine has not helped to eliminate this problem. Relapses and persisters have occurred at the same rate in different trials with good follow-up [35], therefore suggesting that persisters may be the source of relapses. Most of these relapses occurred 6–9 years later. Therefore, long-term follow-up of these patients, especially those with multibacillary disease, is believed to be crucial. PCR techniques are being tried to help better define relapse as reactivation or new infection by means of molecular strain typing. Despite the high rate of drug resistance when dapsone monotherapy was used, multidrug therapy has not, to date, been plagued by this problem. This phenomenon may be partly explained by the central coordination of treatment programs that also supply the drugs recommended in most countries where leprosy is endemic and the WHO recommendations for maximal supervised therapy for a fixed period. This strategy has helped in adherence to accepted treatment regimens with multiple drugs as opposed to potential abuse of single drugs. The current prevalence of resistance to the 3 drugs used is unknown, but it is thought to be low. PCR techniques are being used to try to detect resistance to current and future drugs. DNA sequencing of the M. leprae genome, which is >95% complete [36], may provide further insight into the molecular targets of these drugs. Relapse after multidrug therapy seems to be the result of reactivation of drug-susceptible organisms; therefore, retreatment with multidrug therapy is usually successful.

Standard multidrug therapy for multibacillary disease should be considered for patients with lepromatous disease who have previously been treated with dapsone monotherapy unless there are contraindications. This treatment plan may be especially important for patients who have had ENL, significant nerve damage, or eye involvement. Physicians in the United States who desire information for referral centers or expertise on leprosy can con-
tact the National Hansen’s Disease Program at their Web site at http://www.bphc.hrsa.gov/nhdp.

PREVENTION

Prevention of disease with vaccines based on *M. leprae* or other mycobacteria has thus far not proved to be effective in large-scale clinical trials. BCG vaccination is highly protective against leprosy in some populations [4] but not in others [37]. Repeated doses of BCG vaccine appear to be more effective [4], but this approach may have limited usefulness because of potential adverse reactions in the immunosuppressed patient and the cost of implementation of this therapy. Successful sequencing of the *M. leprae* genome will lead to better understanding of its immunology and perhaps better vaccine candidates.

Dapsone prophylaxis for high-risk contacts of index patients has not proven to be successful. Early detection of subclinical leprosy or the carrier state has also been difficult. *M. leprae* can be detected by PCR analysis in nasal swabs from unaffected individuals exposed to leprosy, but the infectivity and risk of disease in these patients remain to be defined. Because multidrug therapy does not eliminate transmission of leprosy in households [38], identification by PCR analysis (or other methods) of high-risk contacts who would benefit from more effective, future prophylactic regimens deserves further study.

CONCLUSION

The decline in the prevalence of leprosy and the commitment to elimination of leprosy as a public health problem have been matched by a decline in leprosy research. For the reasons delineated in this article, it is unlikely that leprosy will disappear as a health problem and, in fact, leprosy will continue to be seen in countries where it may not be easily diagnosed and treated.

With multidrug therapy, the prevalence rate has been favorably affected; however, it has not had much impact on the incidence rate. Southeast Asia and Brazil continue to be areas where leprosy is highly endemic. PCR and serological techniques have failed to significantly impact the diagnosis of early disease. HIV disease has not affected the rate of diagnosis or outcome of leprosy. Despite better immunologic understanding of the disease, so far, immunotherapy has no role in treatment of leprosy. BCG vaccination remains the most effective prophylactic measure. Fortunately, resistance to multidrug therapy has not been a major clinical problem. The role of persisters needs to be better understood, and more effective modalities of therapy need to be established. It is hoped that there will be a continuing commitment to crucial areas of research in leprosy as we enter the 21st century.

References

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