Ann. Rev. Pharmacol. Toxicol. 1988. 28:231–45

CHEMOTHERAPY OF LEPROSY[1]

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BACKGROUND

Leprosy is a chronic infectious disease of human beings. The predominant clinical manifestations of leprosy, or Hansen's disease, are lesions of the skin, mucous membranes, and peripheral nerves. The disease affects some 10–12 million individuals worldwide, largely in Asia and Africa (1). The comprehensive management of a leprosy patient is complex. Only a relatively small component of that comprehensive medical management consists of chemotherapy directed against the causative organism, *Mycobacterium leprae*. The characteristic, regrettable stigma associated with leprosy comes about not because of skin lesions but because of the nerve damage and the resulting deformities that the disease can cause. It is, therefore, the existing deformities that must be corrected, and the future deformities that must be prevented, if the leprosy patient is to be successfully treated and the stigma of the disease minimized.

M. leprae characteristically involves peripheral nerves, resulting in slowly progressive sensory and motor losses in characteristic clinical patterns. Episodic, immunologically mediated inflammation directed against components of *M. leprae*, the so-called lepra reactions, occurs in up to 50% of leprosy patients and can acutely damage any tissue containing *M. leprae*, particularly peripheral nerves, resulting in acute deformities. A third pattern of deformities results from loss of protective sensation, frequently coupled with abnormal motor function, with resulting traumatization of extremities, open wounds, secondary infection, loss of tissue, etc. The successful medical

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management of leprosy must therefore, as a minimum, (*a*) halt the multiplication of *M. leprae* with appropriate chemotherapy to stop slowly progressive nerve damage and deformities, (*b*) control lepra reactions with appropriate anti-inflammatory therapy when needed to prevent acute deformities, and (*c*) provide a rehabilitative system involving patient education, specialized footwear, specialized tools, and specialized care of secondary traumatic wounds in sensory-denervated extremities to prevent secondary deformities.

The overall management of a leprosy patient is strongly influenced by the degree of resistance an individual patient shows against *M. leprae*. This resistance is thought to be genetically determined (2) and based on varying degrees of cell-mediated immunity against the bacillus. Individuals with strong cell-mediated immunity toward *M. leprae* typically have a localized disease that tends to self-heal. The skin and nerve lesions contain relatively few bacilli, and the tissue response is characteristically a well-developed epithelioid cell granuloma. This is called tuberculoid leprosy. At the other extreme of the leprosy spectrum is the widely disseminated, anergic disease called lepromatous leprosy. This disease does not tend to self-heal, the lesions contain quite large numbers of *M. leprae,* and the characteristic histopathology is that of a foam cell granuloma. Between tuberculoid and lepromatous is a continuous spectrum of disease called borderline leprosy. Borderline leprosy near lepromatous is called borderline-lepromatous, borderline disease in the middle of the spectrum is called mid-borderline, and borderline disease near tuberculoid is called borderline-tuberculoid leprosy. These points on the spectrum have intermediate levels of cell-mediated immunity, bacterial load, and histopathology. As might be expected, the intensity and duration of the required antibacterial chemotherapy differ considerably depending on the classification of an individual patient's disease.

During the course of their disease, up to 50% of leprosy patients develop acute, immunologically mediated inflammatory conditions called lepra reactions. These are of two types (3). In patients with good cell-mediated immunity toward *M. leprae,* i.e. tuberculoid, borderline-tuberculoid, and mid-borderline patients, these take the form of so-called type 1 reactions. Characteristically, they are manifested as inflammation in preexisting lesions of both skin and peripheral nerves. Histologically, these reactions are initially characterized by edema, progressing in some cases to caseation necrosis. The mechanism of these type 1 reactions is thought to be delayed-type hypersensitivity. In lepromatous and borderline-lepromatous patients, who essentially lack cell-mediated immunity against *M. leprae,* the reactions take the form of crops of tender, erythematous skin nodules in areas of high concentrations of bacilli. This is usually associated with fever and commonly is associated with inflammation of other tissues containing high concentrations of *M. leprae* such as the eyes, peripheral nerves, joints, testes,

lymph nodes, etc. Reactions of this type are called erythema nodosum leprosum or type 2 reactions in leprosy (4).

MYCOBACTERIUM LEPRAE

Mycobacterium leprae shares with other mycobacteria a number of phenotypic traits, including acid-fastness, a lipid-rich cell envelope, a lack of known exo- and endotoxins, and a very slow rate of growth. It is, however, unique among mycobacteria in its ability to oxidize dihydroxyphenylalanine (DOPA) (5) and in its pyridine-extractable acid-fastness (6). In addition, *M. leprae* possesses a species-specific phenolic glycolipid-I (PGL-I) antigen that comprises 2% of the bacillary mass (7) and is thought to be involved in the intracellular survival of the bacillus (8). It is genotypically distinct from other mycobacteria with respect to DNA homology (9) and percent guanine plus cytosine (10, 11), and its generation time of 11–13 days (12, 13) is the longest known for any microorganism. Its affinity for Schwann cells of the peripheral nervous system is also unique among bacteria (14, 15). *M. leprae* is the last bacterium of major clinical significance to resist all attempts at cultivation in both cell culture and axenic media. This has impeded all aspects of leprosy research, including the search for effective drugs, and has necessitated the development of unconventional drug susceptibility tests.

METHODS TO FIND ANTIBACTERIAL AGENTS

Clinical Trials

Early antileprosy drugs were developed on the basis of empirical clinical trials in leprosy patients. The first known medication with definite antileprosy activity was chaulmoogra oil. It was first described by Mouat (16), who reported that according to Burmese folklore, the oil had been used to treat leprosy. A similar approach led to the first modern-day treatment of leprosy with Promin, described by Faget et al (17). Promin (glucosulfone sodium), in contrast to the irregular efficacy of chaulmoogra oil, gave excellent results and established the sulfones as the treatment of choice for leprosy—a position they have never relinquished. Similarly, empirical trials of streptomycin were carried out in 1945 (18). In the 20 years that followed the introduction of Promin, a great many drugs were tested in empirical clinical trials usually based on evidence of activity against *M. tuberculosis,* either in vitro, clinically, or in animal models of tuberculosis.

Mouse Footpad Infections with M. leprae

In 1960 Shepard (19) demonstrated that *M. leprae* would multiply to a limited extent in the footpads of immunologically intact mice, thereby making it

possible to test with more scientific rigor the drug susceptibility of *M. leprae*. This animal model also made it possible to determine both primary and secondary drug resistance in *M. leprae* (20). Immunologically intact mice can be used to study the effectiveness of drugs against *M. leprae*. Four different techniques are employed. In the first of these, the drug is administered to the animals continuously from the day of inoculation with *M. leprae*. Growth of the organisms indicates lack of susceptibility to the drug being administered or the presence of drug resistance if the sample of *M. leprae* is from a human skin biopsy. In the second method, bacilli are inoculated and allowed to proliferate for several months. The drug is then administered for a finite period of time, commonly 2 months, and mice are sacrificed at intervals after the drug is discontinued. If the delay in the multiplication of bacilli in the drug-treated animals is the same as the period of drug administration, the drug is said to be bacteriopausal. If the delay in growth of bacilli from drug-treated animals is considerably longer than the period of drug administration, the drug is considered to be bactericidal. A third approach is the proportional bactericidal method. In this method, tenfold dilutions of the bacterial inoculum are given to groups of mice. The drug is then administered for a finite period of time, commonly 2 months, and counts of the bacilli are carried out on the mice 12 months after inoculation. The concentration of infective *M. leprae* remaining after the drug treatment can be estimated. This procedure detects bactericidal activity but cannot differentiate between drugs that are inactive and drugs that are purely bacteriostatic. A fourth technique utilizes immunologically intact mice to detect viable organisms in serial skin biopsies of patients initiating chemotherapy. This technique detects one or more viable organisms per inoculum of *M. leprae,* usually 5×10^3 or 10^4 organisms. The time required for detectable viable organisms to disappear in treated patients is a measure of the rapidity of onset of drug action. [Reviewed by Shepard, 1985 (21)].

A great many other animal models of leprosy have been attempted (22). A number of these have been successful (21). The nine-banded armadillo is the animal model of choice for the production of *M. leprae*. Models of so-called "multibacillary leprosy" that are being used to a limited extent for chemotherapy trials include the neonatally thymectomized Lewis rat (23) and athymic, nude mice (24, 25). Neonatally thymectomized Lewis rats have been used primarily for the detection of persisting viable organisms from clinical biopsies following chemotherapy. Nude mice have been used primarily for determining the activity of individual drugs (26–31).

In Vitro Techniques

The use of animal systems for primary drug screening imposes severe limitations on the number of compounds that can be evaluated. The labor and

expense involved in animal maintenance over a 6–12 month incubation period as well as a requirement for up to 10–15 g of new compounds [for minimal therapeutic dose (MTD) determinations] (32) have prompted the development of relatively rapid in vitro systems that rely on inhibition of bacterial metabolic functions as indices of drug activity. In general, these systems involve the exposure of *M. leprae* to various antimicrobial agents while residing within macrophages or while suspended in axenic (cell-free) media. The metabolic activity of the bacilli is then assessed and compared to drug-free controls.

The use of human or mouse macrophage cell cultures provides the bacilli with a relatively hospitable environment and simulates, to some extent, in vivo intracellular drug penetration and concentration. The most well-developed system involves pulsing phagocytosed bacilli with ^{3}H-thymidine in the presence and absence of drugs and then determining the relative uptake of the label by the bacilli, in comparison to heat-killed controls. This system has been used for the evaluation of clofazimine derivatives (33) and for the rapid determination of dapsone resistance in clinical isolates (34). The latter has shown good agreement with mouse footpad assays and can be performed in a microculture plate (35), requiring only 10^5 bacilli and 5×10^5 macrophages per assay. Thus, replicate assays can easily be set up with the bacilli recovered from a patient skin biopsy and with the peritoneal macrophages from a single mouse. *M. leprae* residing within murine macrophages also have been shown to incorporate ^{14}C-palmitic acid into the *M. leprae*-specific antigen, phenolic glycolipid-I (PGL-I), an activity that is completely suppressed in the presence of rifampin (36). Over 25 compounds have been examined in this system (37), and results obtained have shown good overall agreement with the axenic-ATP system (38) described below. While technically more cumbersome to perform than the ^{3}H-thymidine uptake system, assays of PGL-I synthesis are less susceptible to interference by low level contamination (because of its species specificity) and should also provide the potential for identifying new agents that may directly inhibit PGL-I synthesis. A number of other assays are being developed for assessing viability of drug-treated *M. leprae* residing within macrophages (39). Two of these involve changes in the macrophage membrane. Phagocytosis of live *M. leprae* effects a reduction in Fc receptors as measured by rosetting between macrophages and antibody-sensitized sheep erythrocytes and by a reduction in the amount of sialic acid on the macrophage membrane that can be removed with neuraminidase. Other assays involve a reduction in hydrolysis of fluorescein diacetate by drug-treated *M. leprae* (determined by either fluorescence microscopy or spectrofluorometry) and a reduction in the uptake of labeled uracil. Although possessing no readily apparent advantages over those described above, these assays have potentially expanded the number of methodologies available for determining drug susceptibility of phagocytosed *M. leprae*.

Axenic systems are much less cumbersome than the macrophage systems and are not subject to potential problems associated with metabolism and variation of host cells. Dapsone and rifampin treatment of extracellular bacilli reportedly inhibit the uptake of radiolabeled thymidine and DOPA (40). The rapid auto-oxidation of the latter is probably at least partially responsible for the absence of further reports of its utility in drug susceptibility testing. Although the sensitivity of thymidine uptake to these drugs in *M. leprae* has been independently confirmed (41), purines, which are taken up at 6–20 times the rate of uptake of pyrimidines, may be preferential substrates in such a system. Hypoxanthine incorporation rapidly ceases in the presence of dapsone, rifampin, and desoxyfructoserotonin (42) and has yielded minimal inhibiting concentration (MIC) data for dapsone, clofazimine, and brodimoprin (43). The measurement of intracellular ATP using the firefly bioluminescence technique has recently been employed by a number of laboratories as a rapid index of viability of *M. leprae* harvested from armadillos (44), from nude mice (45), and from patients following drug treatment (46), and to evaluate the potential of culture media (47–48). A dose-dependent accelerated rate of ATP decay was first described in extracellular *M. leprae* incubated in buffer in the presence of clofazimine (44). In the most comprehensive study to date, ATP analysis was employed as a means of screening 23 established antimicrobial agents for anti-*M. leprae* activity (38). Nude mouse–derived *M. leprae* were incubated axenically in a modified Dubos medium that supported a rate of ATP decay sufficiently slow to allow for the detection of accelerated rates in the presence of effective drugs. In general, the results in this system agreed well with those previously found in mouse footpad studies (49, 50). In addition, the axenic ATP system appeared suitable for assessing comparative activities of new structural analogs of clofazimine. Somewhat surprisingly, erythromycin was found to possess potent direct activity against *M. leprae* (discussed below). Recent studies in our laboratory have identified axenic conditions supporting incorporation of ^{14}C-palmitic acid into the phenolic glycolipid-I of *M. leprae* (51). This axenic incorporation of palmitic acid into PGL-I offers the same advantages as discussed above for this activity in *M. leprae* residing in macrophages while reducing the complexity of the incubation system. A laser microprobe mass analyzer (LAMMA 500, Leybold-Heraeus, Köln, Federal Republic of Germany) that determines drug susceptibility of *M. leprae* by changes in the intracellular sodium/potassium ratio may also be used to detect new anti-leprosy drugs (52). While somewhat cumbersome for clinical application (53), this technology allows examination of drug-kill kinetics while requiring very low numbers of cells.

Although of great utility in identifying potentially useful drugs, the assays described above are either too cumbersome for routine use in clinical drug susceptibility testing or require more bacilli than can be obtained from punch

skin biopsies. We have recently observed the rapid oxidation of palmitic acid to carbon dioxide by nude mouse-derived *M. leprae* (54), an activity exploited clinically in the automated radiometric detection of drug susceptibility in cultivable mycobacteria (55) (BACTEC, Johnston Laboratories, Inc., Towson, Maryland). Bacilli exposed to a variety of anti-leprosy drugs for 1–2 weeks under axenic conditions displayed significantly reduced rates of $^{14}CO_2$ evolution upon subsequent addition of ^{14}C-palmitic acid. This activity can be readily detected with 10^6 bacilli, thus suggesting its potential for use in clinical susceptibility testing.

CHEMOTHERAPEUTIC REGIMENS IN LEPROSY

The three basic approaches to the chemotherapy of leprosy are monotherapy, various combination regimens, and the regimens recommended by the World Health Organization for control programs (56). Monotherapy is no longer recommended because of the development of drug-resistant *M. leprae*. On the other hand, in many parts of the world monotherapy is widespread, and dapsone is the drug predominantly used. A variety of combination regimens are utilized, either as standard regimens or as trial regimens. Current recommendations in the United States for adult patients are dapsone plus rifampin for patients infected with dapsone-sensitive *M. leprae* and clofazimine plus rifampin for patients infected with dapsone-resistant *M. leprae*. More specifically, for dapsone-sensitive disease in patients with so-called paucibacillary leprosy (indeterminate, tuberculoid, and borderline-tuberculoid), dapsone is given in a daily dose of 100 mg for 4–7 years, depending on the classification, and rifampin is given in a daily dose of 600 mg for the first 6 months of treatment. If a paucibacillary patient is infected with dapsone-resistant *M. leprae*, a daily dose of 50–100 mg of clofazimine is substituted for dapsone. In so-called multibacillary leprosy patients (mid-borderline, borderline-lepromatous, and lepromatous), dapsone, 100 mg, is given daily for life for patients infected with dapsone-sensitive organisms. For the first 3 years, rifampin is given in combination with dapsone in a dosage of 600 mg daily. For patients infected with dapsone-resistant *M. leprae*, clofazimine, 50–100 mg daily, is substituted for dapsone and given for life. These combination regimens have been used in the U.S. since 1971 with excellent results. Mouse footpad drug sensitivity testing has indicated a steady decline in the rate of detection of secondary sulfone resistance, as well as a decline in the rate of low level primary sulfone resistance of newly diagnosed, previously untreated patients.

The recommendations of the World Health Organization (WHO) for control programs (56) are based on a number of considerations, including the practical constraints under which a number of field programs have had to

work. It was presumed that slit-skin smear facilities can be made generally available, but that precise classification of an individual patient based on detailed clinical and histopathological criteria might be impossible. Thus, patients were divided into two groups, paucibacillary and multibacillary, based on the so-called bacterial index of slit-skin smears. A bacterial index of $< 2+$ at all sites defines a paucibacillary case and a bacterial index of 2+ or more at any site defines a multibacillary case. The presumption is that sulfone resistance is common, both primary and secondary, and that any regimen should be effective in both dapsone-resistant and dapsone-susceptible disease. The aim of therapy is to interrupt transmission of the infection and to eliminate all viable *M. leprae* from the body in as short a period of time as possible. Low percentages of relapses after discontinuation of treatment are acceptable. Ideally, drug regimens should be fully supervisable in order to ensure good patient compliance. Finally, costs were taken into consideration.

The WHO recommended regimen (56) for paucibacillary patients consists of dapsone, 100 mg daily for 6 months, unsupervised, plus rifampin 600 mg once monthly for 6 months, supervised. Treatment is then discontinued. For multibacillary patients, dapsone, 100 mg daily, with clofazimine, 50 mg daily, is given unsupervised; rifampin, 600 mg, and clofazimine, 300 mg, are both given once monthly, supervised. For multibacillary patients, treatment is continued for at least 2 years and preferably until bacterial negativity has been attained, as measured by slit-skin smears. For further discussion, see Hastings (1987) (57), Jacobson (1987) (58), and Jacobson (1985) (59).

INDIVIDUAL DRUGS FOR LEPROSY

Dapsone

Dapsone (4,4'-diaminodiphenyl sulfone, DDS) has replaced earlier sulfones used in leprosy. Like the sulfonamides, dapsone is an analog of *p*-aminobenzoic acid (PABA) and inhibits the de novo synthesis of folic acid by *M. leprae*. The drug is essentially bacteriostatic because of this mechanism of action, although it appears to be weakly bactericidal in *M. leprae* infections in the mouse footpad (60). Dapsone is almost completely absorbed from the gastrointestinal tract, mainly from the upper part of the small bowel. Free dapsone is distributed throughout total body water. The drug is 70–80% bound to plasma albumin, and its major metabolite, monoacetyl-DDS (MADDS), is 98–100% bound to albumin (61). Dapsone undergoes various metabolic reactions in the liver, the most prominent of which is acetylation. Individuals are genetically polymorphic with regard to their ability to acetylate dapsone, but acetylator status does not appear to have significant effects on the overall half-life of the drug (62). The drug is mainly excreted in the

urine as metabolites. The half-life of dapsone in human plasma is quite variable with a mean of approximately 28 hours (62).

The predominant side effects of dapsone are hemolytic anemias, particularly with glucose-6-phosphate dehydrogenase deficiencies. The dapsone (DDS or sulfone) syndrome is a rare clinical syndrome that usually develops within 6 weeks of the start of therapy. The syndrome consists of exfoliative dermatitis and/or other skin rashes, hepatosplenomegaly, fever, generalized lymphadenopathy, and hepatitis (59). Agranulocytosis is rarely seen with dapsone (63). In leprosy, the adult dose of dapsone is 100 mg daily. There is evidence that maximum subtoxic doses should be administered in order to minimize the possibility of *M. leprae* developing sulfone-resistance (64).

Rifampin

A derivative of rifampin, rifamycin S-V, was first used as an intramuscular preparation in leprosy treatment in 1963 (65). Rifampin was first used in leprosy treatment in 1968 (66). The chemistry, mechanism of action, and toxicities of rifampin are well known. Rifampin induces the metabolism of dapsone (67), but in the usual clinical setting this is of little significance. Rifampin is rapidly bactericidal for *M. leprae*. When used as monotherapy, resistance may develop after a period of 3–4 years (68).

Clofazimine

Clofazimine was first used in leprosy treatment in 1962 (69). Clofazimine is a phenazine derivative with antibacterial and anti-inflammatory effects, but its mechanism of action is not known with certainty. The drug is administered orally in a micronized form, and in the usual clinical dose of 100 mg approximately 70% is absorbed. Clofazimine has a complex pattern of distribution with high concentrations found in the reticuloendothelial system, in subcutaneous fat, and in the distal small bowel at the site of absorption. The overall half-life of elimination of clofazimine has been estimated to be about 3 months (70, 71). The most prominent adverse effect of clofazimine is a dose-related skin pigmentation caused by the accumulation of the drug itself. Toxicity also occurs in the gastrointestinal tract, since crystals of the drug are deposited in the distal small bowel and in the draining mesenteric lymph nodes. This causes disturbances of small bowel motility with resulting anorexia, nausea, vomiting, crampy abdominal pain, diarrhea, and weight loss. These gastrointestinal toxicities are dose-related (72). Despite the fact that clofazimine has been used for many years as a monotherapy in leprosy, there are only two reports of possible clofazimine-resistant leprosy cases (73, 74).

Ethionamide/Prothionamide

Ethionamide and prothionamide are essentially identical in their activities and toxicities. Ethionamide has been used occasionally to treat leprosy for over 20 years. More recently, interest has increased because of the desire to find other drugs useful in combination regimens. Ethionamide is bactericidal against *M. leprae* in the mouse footpad system. It is readily absorbed from the gastrointestinal tract and has a half-life of approximately 3 hours. It is metabolized in the liver to the sulfoxide and then to inactive metabolites. Excretion is via the kidney. The most common side effects of ethionamide are gastrointestinal and hepatotoxicity. Hepatotoxicity is relatively rare when the drug is used alone, but it is markedly increased when ethionamide is given on a daily basis in combination with daily rifampin. Both drugs are hepatotoxic, and this hepatotoxicity is additive. A dose of 250–500 mg daily is used to treat adult leprosy patients. The drug should always be used in combination since, like rifampin, monotherapy results in the development of resistance within a few years of treatment (59).

Thalidomide

Thalidomide was widely used as a sedative-hypnotic between 1957 and 1961. In 1961 the drug was shown to be associated with characteristic congenital malformations (phocomelia) when taken by pregnant women (75). In 1965 the drug was demonstrated to be active in type 2 or erythema nodosum leprosum-type reactions occurring in lepromatous leprosy (76, 77). The mechanism of action of thalidomide in erythema nodosum leprosum is not known with certainty. The drug appears to inhibit de novo synthesis of IgM-type antibodies and to inhibit the chemotaxis of human neutrophils (78). Thalidomide has no antibacterial effect on *M. leprae* and is not active in type 1 lepra reactions. Thalidomide is well absorbed from the small intestine and distributed throughout body water. It undergoes nonenzymatic hydrolysis in a pH-dependent fashion in the blood. The drug and its major hydrolysis products are excreted in the urine. The half-life of the drug is approximately 3.5 hours. The major universal side effect of thalidomide is embryopathy, if the drug is taken by a pregnant woman between 35 and 50 days after the last normal menstrual period. The only other side effect of significance is a peripheral neuropathy (79). Thalidomide is the drug of choice for erythema nodosum leprosum reactions occurring in male patients and in females who do not have childbearing potential (80).

FUTURE PROSPECTS

While the existing anti-leprosy drugs discussed above are unquestionably effective, they are limited in number and only one, rifampin, is rapidly

bactericidal. These factors, along with the existence and potential for development of drug resistance, have led to an ongoing search for new promising anti-leprosy agents. In vitro metabolic assays for determining drug susceptibility in *M. leprae* residing either within macrophage cells or existing free in the axenic media should prove useful in rapidly and inexpensively identifying new anti-leprosy agents. They offer the prospect of analyzing large numbers of compounds and determining the relative effects of intracellular drug concentrations by comparing minimum inhibitory concentrations in both intracellular and extracellular bacilli. In addition, simple, sensitive radiometric assays such as the macrophage microculture/thymidine system and the axenic/palmitic acid oxidation system (with the potential for adaption to the BACTEC system) may make routine clinical drug susceptibility testing a reality in the not-too-distant future.

Currently, there is much interest in the potential of the fluoroquinolines, in part due to their activity against cultivable mycobacteria (81). Ciprofloxacin has demonstrated activity against *M. leprae* in a number of in vitro test systems (37–39). Pefloxacin and ofloxacin, however, have demonstrated superior activity in the mouse footpad system (82–84), most likely because of their more favorable pharmacokinetics (85).

Recently, a number of phenazines have been synthesized that, unlike clofazimine, do not result in skin pigmentation. Two of these compounds, B826 and B3785, have shown activity roughly equivalent to clofazimine in the mouse footpad system (86) and have also shown equivalent or superior activity in the axenic/ATP system (38). Further studies should determine if these compounds can effectively replace clofazimine in multi-drug regimens.

The ribosome is a site that has yet to be exploited in the chemotherapy of leprosy. Compounds acting at this locus should thus be considered good candidates for inclusion in multi-drug regimens with existing anti-leprosy drugs. Recent studies have revealed the potential of two protein synthesis inhibitors, minocycline and erythromycin. The former has shown activity in both the axenic/ATP system (38) and in the macrophage/PGL-I synthesis system (37), as well as showing good activity in the mouse footpad (87). However, the nontoxic macrolides are considerably less expensive, more thermo-stable, and show the highest intracellular/extracellular concentrations of any antibiotics (88). They would thus appear to have greater potential as anti-leprosy drugs were it not for their fairly poor pharmacokinetic properties. Erythromycin has shown potent activity in repeated experiments in our laboratory in the axenic/ATP and macrophage/PGL-I systems, as well as in the axenic/palmitate oxidation system (54). In addition, two new macrolides, RU-965 (89) and TE-031 (90, 91), both possessing superior pharmacokinetics, have shown very potent activity in both of these in vitro systems (92). Mouse footpad experiments (now in progress) with these compounds should

indicate their potential clinical utility in combination chemotherapy regimens.

In the near future, the efficacy of current WHO recommended treatment regimens (56) should be either established or shown to require modification. Controversy in this area centers around the recommendation to discontinue all treatment after 6 months in the case of paucibacillary leprosy and after 2 years in the case of multibacillary leprosy. Data on relapse rates following discontinuation of treatment are now being gathered for both types of patients from various parts of the world. Decisions will be required as to whether or not these relapse rates are acceptable in the context of each individual leprosy control program.

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