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D. EXPERIMENTAL THERAPY

A Survey of the Drugs with Activity Against *M. leprae* in Mice

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Mouse footpad inoculation is used in many ways now in studies of antileprosy drugs. Here I would like to review only one aspect, that of determining the spectrum of drugs active against *M. leprae* and the type of activity exerted by three of the most effective drugs.

In tests of drugs against *M. leprae* in mice, two schedules of drug administration have been used for the most part: first, the continuous method, whereby the drug is given from the day of inoculation until the end of the experiment; second, the kinetic method, in which the drug is given only for a limited period, for example, from the 70th to 140th day after infection. When the first chemotherapy experiments were started 10 years ago ([27]), we felt that perhaps only a few drugs would be found active against *M. leprae* in mice; so we selected a design that would not be likely to miss detecting a drug with any activity at all. Our supposition was that the few drugs that would be found active in mice could then be tried clinically to select those with genuine value in human therapy. We found, however, that many were active in mice, more than could be compared in clinical trials. Consequently, it seemed that a more rigorous test of antibacterial activity was needed, one that could differentiate the drugs that had a good chance of being useful in man. Two solutions seemed possible: first, a titration of the active drugs to find those with low minimal effective dosages; second, a modification of the experimental design that would allow the detection of drugs with a bactericidal effect. In the latter approach, called the kinetic method, the drug is administered for a limited period at a time near the beginning of the logarithmic phase of bacterial growth in the mouse footpad. After the drug is stopped, one observes if and when subsequent bacterial growth appears. Drugs that are merely bacteriostatic can be distinguished from those that are bactericidal ([21, 25]). A bactericidal-type result can, of course, be produced by a drug, such as B.663, that persists in the tissues for a long period, but otherwise the distinction between bacteriostatic and bactericidal drugs in mice seems reliable. When a drug is completely bactericidal during the usual period of administration, say 70 days, it needs then to be tried for a shorter period; this point will be illustrated later by the results with rifampin.

The results in Tables 1-8 have been collected from the literature and from unpublished information from our laboratory, the laboratory of Dr. Louis Levy in San Francisco, or that of Dr. G. R. F. Hilson in London. We are indebted to Dr. Levy and Dr. Hilson for allowing us to include their results. Information was available on 86 drugs. Incidentally, we would appreciate it if authors would make other unpublished results available for incorporation into future versions, which we intend to circulate at frequent intervals to interested leprosy scientists (via Leprosy Scientific Memoranda) and perhaps also at less frequent intervals in publications. For the same reason, we would appreciate having errors pointed out to us.

Table 1 contains data on sulfones. The

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TABLE 1. *Sulfones.*

Drug	Activity by continuous method[a, c]	Activity by kinetic method[b]
1. DDS (dapsone)	0.1–0.0001% A([6, 13-17, 22, 23, 26-28, 30, 32]); 0.00001% A([16, 22, 26, 30, 32]); I([15-17, 22, 23, 26, 30])	0.01–0.0001% C([21, 25]); 0.00001% I([21, 25]); 0.0001–0.000025% S([26])
2. Solapsone	2.5 mgm./kgm. A, 0.25 mgm./kgm. P([6])	
DFD (di-formyl DDS)		0.1% C([25]); 0.01–0.0001% C, 0.00001% I([26])
4. DADDS (di-acetyl DDS)	200–6 mgm./kgm./2 mo A, 1.5 mgm./kgm./2 mo P, 0.4–0.1 mgm./kgm./2 mo I([23])	
5–10. Six other repository sulfones	200 mgm./kgm./2 mo A([23])	

[a] A = active (complete suppression of growth of *M. leprae*), I = Inactive, P = Partial suppression of growth.
[b] C = bactericidal, S = bacteriostatic, I = inactive.
[c] In this and the following tables, the dosage is expressed as follows: "%" refers to the amount of drug added to the diet, and "mgm." or "mgm./kgm.", to the amount of drug given parenterally by the subcutaneous route, except when it was given intraperitoneally (IP). The injections were daily unless otherwise stated.

central fact here is the sensitivity of *M. leprae* to DDS. All strains from untreated leprosy patients tested so far have been sensitive to 0.0001 per cent DDS in the diet. Our laboratory has now observed 17 strains of *M. leprae* with this sensitivity. A few strains are sensitive to 0.00001 per cent DDS in the diet. The very small minimal effective dosage presumably explains the therapeutic effect of other more complicated sulfone preparations, which were used widely in human therapy at one time; usually they were employed in large dosage, and a contamination of only a few per cent with DDS, or the metabolic conversion to DDS of a small percentage of the dosage, would be enough to explain their effectiveness. Solapsone may owe its activity to one of these two causes, but decisive studies have not yet been done. Oral DFD is converted almost completely to DDS in the mouse ([11]). DADDS releases DDS slowly ([7, 11]), and the other six repository sulfones presumably do the same.

TABLE 2. *Sulfones and structurally related compounds*([9]).

Drug	Activity by kinetic method[a]
11–23. Sulfanilamide; 4,4′-methylene dianiline; 4,4′-diaminodiphenylamine; 4,4′-diaminodiphenylether; 4,4′-diaminodiphenyl ketone; 4,4′-diaminodiphenyl disulfide; 3,3′-diaminodiphenylsulfone; 2,4′-diaminodiphenylsulfone; 4-amino, 4′-methoxydiphenylsulfone; 4-amino iphenylsulfone; 4-amino, 4′-bromodiphenylsulfone; 4-aminophenylpyridylsulfone; thiazolsulfone (promizole)	All equimolar with 0.01% DDS I
24. 4,4′-diaminodiphenylsulfoxide	0.0045% C
25. 4,4′-diaminodiphenylsulfide	0.009% C
26. 4-aminoethyl, 4′-aminodiphenylsulfone	0.011% C
27. 4-acetylamino, 4′-aminodiphenylsulfone (MADDS)	0.003–0.0003% C
28. 4-amino, 4′-nitrodiphenylsulfone	0.011% S
29. 3,4′-diaminodiphenylsulfone	0.01% S

[a] C = bactericidal, S = bacteriostatic, I = inactive

TABLE 3. *Inactive drugs*[a].

1–13. Sulfones and related compounds (Nos. 11 to 23 in Table 2), equimolar with 0.01% DDS, k[9]
14. *p*-Aminobenzoic acid, 1.0% k[26]
15. Etisul, 0.5% c[13, 28]
16. Ethambutol, 0.25% c[28]
17. Morphazinamide, 0.03% c[6]
18. Pyrazinamide, 0.5% c[28]
19–20. Piperidines ABT 29666 and ABT 38396, 0.01% c[26]
21. Cycloguanil pamoate, 400 mgm./kgm./2 mo c[23]
22. PAM 1392 (2,4-diamino-6-(3,4-dichloro benzylamino)-quinazoline,) 0.1% k[25]
23. Trimethoprim 0.1% k[26], 0.1% c[8]
24. Amicetin, 0.01% k[26]
25. Amphotericin B, 10 mgm./kgm., IP thrice weekly, k[9]
26. Lincomycin, 0.1% k[26]
27. Phosphonomycin, 0.3% k[26]
28. Tetracycline 75 mgm./kgm. c[6]; 0.03 g/l drinking water c[26]
29–35. Indigosulfonate, indigo tetrasulfonate, methylene blue, new methylene blue, phenosafranine, thionine, thymol indophenol, all equimolar with 0.01% B.663, k[9].
36. Poly I: poly C, 7.5 mgm./kgm. IP, thrice weekly c[10]
37. Chlorpromazine, 0.025% k[9]

[a] c = continuous method, k = kinetic method

In Table 2 some results of Dr. Levy are given. His investigation of the structure-activity relationships among sulfones and related compounds so far can be said to confirm early suppositions based on results with cultivable mycobacteria, namely, that activity depends on the presence of a diphenyl sulfone with amino groups in the 4-positions. Compounds 24, 25, and 26 presumably were converted to DDS in the body. The conversion of MADDS to DDS has been demonstrated in mice (and in man). The result with compounds 28 and 29 may have come from contamination with DDS.

Table 3 lists the inactive preparations. The sulfones have already been discussed. PABA was tried in an experiment testing it for ability to antagonize DDS (it was able to do so partially). Etisul, an ethyl mercaptan, was once employed enthusiastically in leprosy, but is not used much now. Ethambutol and pyrazinamide (and morphazinamide which gives rise to it) are effective against tubercle bacilli in the mouse. Compounds 19 and 20 are new drugs synthesized by Elslager *et al.* [5]. They are azo derivatives of tetrahydronaphthylaminopropylpiperidine. Chang found them effective against *M. lepraemurium* [2]. Compounds 21-23 are antimalarials with antifolate actions. Compounds 24-28 are antibiotics with broad spectra; we will return to lincomycin. Compounds 29-35 are dyes with oxidation-reduction capacities, and they were tested by Levy in a study of the mechanism of action of B.663. Poly I:poly C is an efficient interferon inducer; apparently interferon does not inhibit the multiplication of this intracellular microorganism.

TABLE 4. *Drugs partially active by continuous method plus those active by continuous method and inactive by kinetic method.*

Partially active by continuous method
1. Cycloserine, 0.5%[27]
2. Gentamycin, 165 mgm./kgm.[6]

Active by continuous method and inactive by kinetic method[a]
1. Vadrine, 0.1% c[6], 0.1% k[26]
2. Isoniazid, 0.01% c[6, 27], 0.01% k[9, 21]
3. Viomycin 100 mgm./kgm. c[6], 3 mgm. k[26]

[a] c = continuous method, k = kinetic method.

The results in Table 4 are largely self-explanatory. All of these drugs had been reported to have some degree of activity against *M. leprae* in mice.

In Table 5, the first 8 compounds are sulfones already discussed. The repositories were not tested by the kinetic procedure because the duration of persistence of these drugs in the tissues was not accurately known. We will discuss later the long-

TABLE 5. *Drugs found active by continuous method, but not tested by kinetic procedure*[a].

1. Solapsone, 2.5 mgm./kgm. A, 0.25 mgm./kgm. P[6]
2. DADDS, 200–6 mgm./kgm./2 mo A, 1.5 mgm./kgm./2 mo P, 0.4 mgm./kgm./2 mo I[23]
3–8. Six other repository sulfones, 200 mgm./kgm./2 mo A[22]
9. Sulfamethoxypyridazine (kynex, midicel, sultirene), 0.1% A[13]
10. Sulphormethoxine (sulphadoxine, fanasil), 0.01–0.04% A[6, 14]; 0.04% A, 0.004% I[3]
11–13. Ba-22'330, Ba-36'233, Su 2709, 0.1% A[16]
14. Su 3068, 0.06% A[6]
15. Thiocarlide (isoxyl), 0.03% A[8]
16. AW 16'1989 (isobutanol ester of carboxylated thiocarlide), 0.1% A, 0.01% I[8]
17. Amithiozone (TB1), 0.1% P[28], 0.2% A[14], 0.1% A[6]
18. Rifamycin, 150 mgm./kgm. A[6]
19. 20 541 RP 0.1% A, 0.03% I[8]

[a] A = active, P = partially active, I = inactive

acting sulfonamides, compounds 9 and 10; the thioureas, 11-16; and rifamycin, 18. Amithiozone is another drug no longer widely used in leprosy. Compound 19 is a polypeptide antibiotic with activity for tubercle bacilli.

In Table 6 are listed the compounds that are merely bacteriostatic by the kinetic method. Although some of these drugs were not tested by the continuous method, presumably all 11 of them would have been completely active by that method. Thiambutosine, although resistance to it develops in patients rather quickly, is still used in some places for leprosy in patients who develop serious lepra reactions and ENL when given DDS. Some leprologists, however, believe that ENL is a reaction to bacterial killing, and they try to maintain a cover of DDS while moderating the severity of the reactions with corticosteroids. Probably the other thioureas of Table 5 should be tested by the kinetic method. The results with PAS, capreomycin, and streptomycin illustrate the difficulties in predicting results with leprosy bacilli from those obtained with tubercle bacilli. Clindamycin and U-24729A are semi-synthetic derivatives of lincomycin with greatly increased activity against other bacteria. They are more active than lincomycin against *M. leprae*, too, but not sufficiently so to be more than bacteriostatic. Methimazole and 5-n-heptyl-2-thiohydantoin are thyroid depressants; the former was once used in the treatment of leprosy. Their activity in mice was slight and questionable. It was surprising to learn that the product of chaulmoogra oil was definitely active.

Table 7 is a list of drugs giving bactericidal-type results by the kinetic method. We will return to DDS, B.663, and rifampin. Drugs 2-6 are probably active by virtue of their conversion in the body to DDS. Sulfadimethoxine is the only long-acting sulfonamide tested by this method; it would not be surprising if others were also bacter-

TABLE 6. *Drugs found bacteriostatic by kinetic method*[a].

1. 4-amino, 4'-nitrodiphenylsulfone, 0.011% Sk[9]
2. 3,4'-diaminodiphenylsulfone, 0.01% Sk[9]
3. Thiambutosine, 0.1% Ac[6, 12, 14, 15,] Ic[12, 28] 0.1% Sk[9, 21]
4. Crude Na^+ salts of chaulmoogra fatty acids, 136 mgm./kgm. IP, thrice weekly, Sk[9]
5. Aminosalicylic acid (PAS), 0.6% Ac[27], 0.06% Ac[6], 0.6% Ik[21], Sk[26]
6. Capreomycin, 10 mgm. Ac[20], 25 mgm./kgm. Ac[6], 10 mgm. Sk[25]
7. Streptomycin, 2 mgm. Ac[28], 2.5 mgm./kgm. Ac[6], 2 mgm. thrice weekly Sk[21]
8. Clindamycin, 0.1% Sk[26]
9. U-24729 A, 0.05% Sk[26]
10. Methimazole, 0.049% Sk[9]
11. 5-n-heptyl-2-thiohydantoin, 0.16% Sk[9]

[a] A = active; I = inactive; S = bacteriostatic, c = continuous method, k = kinetic method

TABLE 7. *Drugs giving bactericidal-type results by kinetic method*[a].

1. Dapsone, 0.1–0.0001% Ac([6, 13-17, 22, 23, 26-28, 30, 32]), 0.00001% Ac([16, 22, 26, 30, 32]), Ic([15-17, 22, 23, 26, 30]); 0.01–0.0001% Ck([21, 25]); 0.00001% Ik([21, 25]); 0.0001–0.000025% Sk([26])
2. DFD, 0.1% Ck([25]); 0.01–0.0001% Ck, 0.00001% Ik([26])
3. 4,4′-diaminodiphenylsulfoxide, 0.0045% Ck([9])
4. 4,4′-diaminodiphenylsulfide, 0.009% Ck([9])
5. 4-aminoethyl,4′-aminodiphenylsulfone, 0.011% Ck([9])
6. 4-acetylamino, 4′-aminodiphenylsulfone, (MADDS) 0.003–0.0003% Ck([9])
7. Sulfadimethoxine (Madribon), 0.1–0.03% Ac([6, 14]); 0.01% Ac, 0.001% Ic([8]); 0.1% Ck([26])
8. B.663 (clofazimine), 0.01–0.006% Ac([6, 28]); 0.01–0.0001% Ck, 0.00001% Ik([24]); 0.01–0.001% Ck, 0.0001% Ik([26])
9. B.1912, 0.01–0.001% Ac, 0.0001% Pc([8]); 0.01–0.001% Ck, 0.0001% Ik([26])
10. Ethionamide, 0.2% Ck([25]); 0.1% Ck, 0.01% Sk, 0.001% Ik([24])
11. Rifampin, 0.01–0.0025% Ac([18]), 0.0003% Ac, 0.0001% Pc([8]), 0.01% Ck, 0.001% Ik([26])
12. Streptovaricin, 0.06% Ac([6]), 0.06% Ck([26])
13. Cephaloridin 300 mgm./kgm. Ac([6]), 10 mgm. Ck([26])
14. 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole, Ck([9])

[a] A = active, P = partially active, I = inactive, C = bactericidal, S = bacteriostatic, c = continuous method, k = kinetic method

icidal. Through measurements of mouse blood levels, Ellard, Gammon, and Rees ([3]) have recently estimated the minimal inhibitory concentrations for *M. leprae* of sulfadimethoxine and sulfadoxine to be 20-35 μg/ml, or about one-fourth to one-fifteenth the blood levels in man achieved by normal dosages. Under field conditions, where drug intake may be irregular, relapse due to the emergence of drug-resistant forms then may be a possibility; drug-resistance here would be serious because cross-resistance to DDS would be expected. B.1912 is a new riminophenazine from Barry and, in a comparative titration, its activity was very similar to that of B.663. Both B.663 and B.1912 are stored in the tissues for long periods and retained there; so without more exact data on persistence of drug, the kinetic method cannot prove that these compounds are bactericidal. However, in lepromatous patients receiving B.663, it has been shown by mouse inoculation that the viability of *M. leprae* drops in a characteristic manner ([29, 31]). Ethionamide was bactericidal at 0.1 percent, but only bacteriostatic at 0.01 percent in the diet; it remains to be seen whether bactericidal levels can be achieved safely in man. The antibiotics streptovaricin and rifampin are related to each other; they both inactivate the DNA-dependent RNA polymerase of bacteria by complexing with the enzyme. In a comparative test, streptovaricin was somewhat less effective than rifampin. Cephaloridin, a semi-synthetic derivative of cephalosporin C, acts through interference with cell-wall synthesis. Compound 14 in the table is a new broad spectrum drug with activity for gram-positive and gram-negative bacteria and for parasites ([1]). At present we do not know whether it persists in the tissues.

Among these 14 bactericidal-type drugs there are at least five distinct mechanisms of action. Single-drug therapy, although successful in leprosy with DDS, may not be sufficient with other types of drugs, and combination-therapy involving drugs with different mechanisms of action needs to be considered. Probably combinations should first be tried in mice in order to discover unexpected antagonisms, and studies of various combinations are in progress in our laboratory.

Table 8 summarizes the methodological experience to date. Of the 86 drugs tested, 49 had some activity for *M. leprae*. There is an obvious bias, if you will, because activity by one compound calls for investigation of similar compounds. Nevertheless, it is clear that activity against *M. leprae* is common among antibacterial compounds, especially among antimycobacterial compounds. There are two lessons from this observation: (a) the metabolism of *M. leprae* resembles in many respects the metabolism of other bacteria, especially mycobacteria–

TABLE 8. *Summary of drug testing.*

1. Inactive	37
2. Partially active by continuous method	2
3. Active by continuous and inactive by kinetic method	3
4. Active by continuous, not tested by kinetic method	19
5. Bacteriostatic by kinetic method	11
6. Bacte icidal by kinetic method	14
Total	86

hence, the cultivationists should take heart, and (b) future drug searches should continue to concentrate on drugs with broad antibacterial spectra, especially on those whose spectra extend to mycobacteria. The other important observation from the table is that the kinetic method appears to serve its intended purpose, which is to reduce the number of drugs for further study without eliminating any drugs of real promise.

To know that a drug is highly active against *M. leprae* is not sufficient information, by itself, to make possible an appropriate design of clinical trials, and I would like next to describe briefly the way studies in mice have been used to work out the chief features of the action against *M. leprae* of the three drugs that are probably the most important in leprosy, DDS, B.663, and rifampin.

With DDS the minimal effective dosage in mice was found to be only 0.0001 per cent in the diet, a dosage which produces about 10 ng DDS/ml. serum (Table 9). Since DDS is apparently well distributed in the blood and tissues, this figure could be taken as an estimate of the minimal inhibitory concentration of DDS for *M. leprae*. An intake of 0.00001 per cent DDS usually is not effective, so the minimal inhibitory concentration presumably lies between 1 and 10 ng/ml. Because *M. leprae* was so sensitive to DDS in mice, one could consider the use of the repository sulfone DADDS, a drug which, in man, is injected every 11 weeks in a dose of 225 mgm. and releases DDS steadily ([7]) in the average amount of 2.4 mgm./day ([33]). In mice the drug was found to be active in very small dosages. DADDS was then tried in man and found to be as active as full dosages of DDS in a short-term clinical trial in the Philippines ([33]). A subsequent long-term clinical trial, being carried out in New Guinea, shows satisfactory therapeutic progress at 750 days ([19]). The results with DDS in mice had led to the prediction that 1 mgm. DDS/day would be therapeutically active in man, and a short-term therapeutic trial by Waters, Rees, and Ellard ([34]) confirmed this prediction. Thus the sensitivity of *M. leprae* in man appears to be the same as it is in mice.

B.663 (clofazimine) has a minimal effective dose in mice of 0.0001 or 0.001 per cent in the diet. However, it is difficult to estimate a minimal inhibitory concentration because of the drug's unusual pharmacokinetics. It is excreted extremely slowly, and it accumulates in the tissues while it is being administered. The concentration varies between tissues and probably from cell to cell. However, the storage properties in the tissues appear to offer some interesting possibilities for spaced administration of drug. In mice we have observed that when 0.01 per cent B.663 in the diet was fed as infrequently as once every 4 weeks, it still was active. A clinical trial now seeks to determine if B.663 is effective in man when administered orally at infrequent intervals. Widely spaced administration would, of course, simplify therapeutic cov-

TABLE 9. *Relationship between DDS dosage and DDS in blood*([11]).

DDS dosage in		Blood concentration
Man	Mouse	
(mgm/day)	(% in diet)	(ng/ml)
100		2000 (avg)
	0.01	560–1066
	0.001	63–97
2.4 (DADDS)		50 (avg)
1.0		18 (avg)[a]
	0.0001	7–14

[a] Concentration in serum[4].

erage in endemic areas, and might have application in chemoprophylaxis.

The outstanding feature of rifampin is its rapid bactericidal effect. The drug produces a pronounced killing effect when given to mice for as little as two days. Rifampin is rapidly eliminated from the body (the half-life is about 3 hours in the mouse and in man); so the effect cannot be attributed to persistence of drug in the tissues. For the same amount of growth delay, DDS must be administered for 60 days or more. Rees, Pearson, and Waters ([18]) have offered evidence, primarily through measurements of the morphologic index, that in humans also rifampin is more rapidly bactericidal than DDS. Parenthetically I should mention that these considerations are not affected by the apparent discrepancy between the minimal effective dosages found in Hilson's laboratory and our own.

I might summarize by saying that the experimental model has served rather better than we expected initially. With appropriate modification in experimental design, the model has had the capacity to select the drugs of greater therapeutic promise from a large list of drugs that seemed to have a good chance for activity against *M. leprae*. In addition, the model has made it possible to work out the chief features of action of the more effective drugs so that, with suitable ancillary data, regimens for man can be tested in designs that take advantage of the particular drug's properties. The net effect appears to be that likely new drugs can be found more rapidly and tested more efficiently with minimal exposure of patients to suboptimal test treatments.

SUMMARY

Enough drugs have now been tested in mice to allow some generalizations to be made about the spectrum of drugs with activity against *M. leprae*. So far 86 compounds have been tested in the mouse footpad system, either by the "continuous" method or by the "kinetic" method. Of the 49 compounds that have been found to have some activity against *M. leprae*, nearly all had already been known to have some activity against some cultivable mycobacterium. Thus overall, the metabolism of *M. leprae* appears to be similar to that of other mycobacteria, and the present reliance on cultivable species in the primary screening of new drugs appears to be justified. In detail, however, activity against *M. leprae* has not been predictable from its activity against any single species. Thus, nine drugs that were active against *M. tuberculosis* were inactive, or only partially active, against *M. leprae*. A methodological improvement in tests against *M. leprae* made it possible to distinguish drugs with greater activity; seven drugs that were active in at least one test by the continuous method of drug administration were inactive or only bacteriostatic by the kinetic method. (In the latter method, drugs are administered for a limited period only, frequently from the 70th to 140th day after infection; a bacteriostatic result is one in which bacterial multiplication is suspended during drug administration but resumes as soon as the drug disappears from the body.) The desired result, bactericidal-type activity, was possessed by the following drugs: DDS (and several other sulfones that are converted to DDS in the body), sulfadimethoxine, clofazimine (B.663), B.1912, ethionamide, rifampin (rifampicin), streptovaricin, cephaloridin, and 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole. Most of these drugs have now been studied further, by determining their minimal effective dosages—etc., and their comparative advantages, in view of the needs in leprosy endemic areas, are discussed. For example, DDS, with a half-life of about 20 hours in man and a very low minimal effective dosage, needs, in a dose of 50 or 100 mgm, to be administered at least once every four to five days to keep the blood level above the minimal inhibitory concentration (2.5 to 10 ng/ml.). The repository sulfone DADDS, however, when injected every 75-77 days, maintains blood levels at an average of 50 ng/ml. Clofazimine, because it is excreted so slowly, probably does not need daily administration, and more widely spaced administration is being tested; as with DDS, the minimal effective dosage is far less than might have been expected from standard dosages. The chief feature of rifampin is the rapidity of its bactericide.

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