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Treatment Failure in Leprosy[1]

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I have been asked to begin a discussion of the causes of treatment failure in leprosy and the technics for detecting failure. In order to narrow the scope of the discussion, I shall limit my remarks to a consideration of the failure of antimicrobial treatment of multibacillary leprosy. I should like to exclude from consideration ENL and borderline reactions, events that may complicate the course of recovery during effective antimicrobial therapy of multibacillary leprosy and that have sometimes been confused with treatment failure. For the moment, I wish to define treatment failure in terms of relapse of the disease process --- that is, the appearance of new lesions or the reactivation of healing or healed lesions associated with evidence of resumption of multiplication of M. leprae after a period of response to treatment, during which there had been killing of the organisms. The simultaneous reappearance of solidly-staining organisms, increase of the BI, and reappearance of mouse infectivity constitute evidence of multiplication.

One cannot readily distinguish on clinical grounds between the two major and mutually exclusive varieties of treatment failure: 1) relapse caused by multiplication of drug-susceptible M. leprae; and 2) relapse resulting from multiplication of drug-resistant organisms. Response to a course of carefully supervised treatment suggests that the patient has relapsed with drug-susceptible organisms, but testing the drug-susceptibility in mice of M. leprae isolated from the patient is required to distinguish with certainty between these two causes of relapse. Relapse with drug-resistant organisms occurs when the drug-resistant individuals, already present in the population of M. leprae before treatment had been started, multiply during treatment. Because it has not been possible to study large populations of M. leprae in the laboratory, important characteristics of M. leprae must be inferred from clinical data and from analogy, primarily with M. tuberculosis. In a recent paper, Dr. Rees and his coworkers have estimated the frequency of the mutation for dapsone resistance to be of the order of 1 in 10^6 to 10^7. The mutations probably occur stepwise, both because the resistance ratio varied among the mutants described by Shepard, and because the risk

[1]Discussion.

of emergence of dapsone-resistant infections differs between patients treated initially with low-dosage sulfones and those treated initially with dapsone in full dosage. Relapse with drug-susceptible organisms occurs when treatment is terminated prematurely. Because the antimicrobial treatment of patients with multibacillary leprosy is not often terminated deliberately, relapses usually occur because the patient lapses treatment, unfortunately a not uncommon occurrence when patients are given responsibility for self-medication.

I have already mentioned the technics for detecting treatment failure; most simply, these are clinical --- the appearance of new lesions and reactivation of old ones --- and laboratory --- evidence of multiplication of M. leprae and drug-susceptibility testing of the isolates of M. leprae in mice. I'd like to spend the time remaining on a consideration of the laboratory methods by which we measure the response to antimicrobial therapy.

In Table 1, I have summarized the changes of the BI and MI and of the results of mouse inoculation during the first four years of effective antimicrobial treatment of a patient with previously untreated multibacillary leprosy and suggested an interpretation of these changes. Dr. Shepard has calculated that a patient beginning treatment with a BI of 5+ harbors a population of about 10^{12} M. leprae; the MI of 10% suggests that 10^{11} of these are viable. During the first few weeks of treatment with rifampicin or the first few months of treatment with DDS, the BI does not change significantly, whereas the MI decreases to a baseline value, and mouse infectivity is lost. At this point (the entry for 3 months in Table 1), the proportion of M. leprae infective for mice has been reduced to less than 1 per 1000. During subsequent treatment, the BI decreases by about one unit per year, indicating a decrease of the bacterial population by one order of magnitude per year. After the number of organisms has become too small to permit mouse inoculation, we cannot be certain about further changes in the proportion of viable M. leprae. At one time, we thought that this proportion must decrease at least as rapidly as the total number of organisms decreases. During the last several years, however, our attention has been drawn to the possibility that the proportion of M. leprae infective for mice may decrease more slowly than does the total number of organisms.

In Table 2, I have attempted to fit into this same format some results recently reported by Dr. Rees. M. leprae recovered after treatment with daily rifampicin for two years multiplied in T+R mice inoculated with larger than usual numbers of organisms. Failure of

TABLE 1. Course of events in responding multibacillary leprosy.

Duration of	Findings			Interpretation	
Treatment (months)	BI	MI	Mouse Inoculation	Total *M. leprae*	Viable *M. leprae*
0	5+	10%	+	10^{12}	10^{11}
1	5+	1%	+	10^{12}	10^{10}
2	5+	< 1%	±	10^{12}	10^{9}
3	5+	< 1%	-	10^{12}	$<10^{9}$
12	4+	< 1%	-	10^{11}	$<10^{8}$
24	3+	< 1%	-	10^{10}	$<10^{7}$
36	2+	< 1%	-	10^{9}	$<10^{6}$
48	1+	Not possible	Not possible	10^{8}	?

TABLE 2. Course of events during rifampicin monotherapy of multibacillary leprosy.

Duration of	Findings			Interpretation	
Treatment (months)	BI	MI	Mouse Inoculation	Total *M. leprae*	Viable *M. leprae*
0	5+	10%	+	10^{12}	10^{11}
3	5+	< 1%	-	10^{12}	$<10^{9}$
12	4+	< 1%	-	10^{11}	$<10^{8}$
24	3+	< 1%	- (small inoculum)	10^{10}	$<10^{7}$
			+ (large inoculum)	10^{10}	$\geq 10^{6}$

multiplication from inocula of 5×10^3 per foot pad suggests that the proportion of viable organisms is smaller than 1 per 1000, whereas multiplication from inocula of 5×10^4 organisms indicates that the proportion of viables is no smaller than 1 per 10,000. The importance of this finding is two-fold. First, the use of larger inocula in suitably immunosuppressed animals may permit us to observe the killing of M. leprae during effective antimicrobial therapy beyond the first 99%. Second, the initial rate of killing of M. leprae in rifampicin therapy is not maintained. Although the first 99% of the organisms are killed within a few days of beginning rifampicin, no more than 90 to 99% of the survivors were killed during the subsequent two years of therapy.

In Table 3, I have summarized the results of a trial of DADDS in New Guinea recently reported by Dr. Russell. In a study of about 30 patients with multibacillary leprosy during DADDS monotherapy, the solid ratio rapidly decreased to less than 1 per 100, whereas the BI decreased more slowly, as expected. After 3 or 4 years of treatment, however, solid M. leprae were again detected in smears prepared from about 20% of the patients. Biopsy specimens from some of these patients were found to contain organisms infective for mice. Although earlier specimens from these patients were not inoculated into mice, the results of other trials of DADDS suggest that the initial 99% kill of M. leprae would have occurred during the first six months of treatment. Because the organisms isolated from the New Guinea patients were susceptible to DDS, these results cannot be explained by multiplication of M. leprae during DADDS therapy. Rather, they suggest that the initial rate of killing is not maintained. The decrease of the population of M. leprae, inferred from the decreasing BI, appears to represent preferential clearing of dead organisms, permitting the proportion of infective organisms to increase to detectable levels.

Finally, in Table 4, I have summarized the demonstration by Dr. Waters of M. leprae infective for mice in specimens obtained from about 50% of patients studied after 10 years of supervised DDS therapy. The total population may be very much smaller than indicated here, because Dr. Shepard's calculation assumed a rather generalized distribution of the organisms. And the proportion of viables may be larger than the tentative figure of 1 per 1000; in many of the cases reported by Dr. Waters, multiplication occurred from very small inocula. Here, also, is evidence that the initial rate of killing of M. leprae is not maintained during therapy, and that clearance of the body burden of organisms occurs primarily at the expense of the dead organisms.

TABLE 3. Course of events during DADDS monotherapy of multibacillary leprosy.

Duration of Treatment (months)	Findings			Interpretation	
	BI	MI	Mouse Inoculation	Total *M. leprae*	Viable *M. leprae*
0	5+	10%	Not Done	10^{12}	10^{11}
12	4+	< 1%	Not Done	10^{11}	$<10^{9}$
24	3+	< 1%	Not Done	10^{10}	$<10^{8}$
36	2+	≥ 1%	+	10^{9}	$\sim 10^{7}$

TABLE 4. Course of events during DDS monotherapy of multibacillary leprosy.

Duration of Treatment (months)	Findings			Interpretation	
	BI	MI	Mouse Inoculation	Total *M. leprae*	Viable *M. leprae*
0	5+	10%	+	10^{12}	10^{11}
12	4+	< 1%	-	10^{11}	$<10^{8}$
24	3+	< 1%	-	10^{10}	$<10^{7}$
36	2+	< 1%	-	10^{9}	$<10^{6}$
48	1+	Not possible	Not possible	10^{8}	$<10^{5}$
120	0-1+	Not possible	±	$\leq 10^{8}$ (?)	$\geq 10^{5}$ (?)

In this discussion, I have dealt only indirectly with the issue of treatment failure, while concentrating on the problem of survival of drug-susceptible M. leprae during apparently adequate chemotherapy. Until recently, perhaps because of the limitations of our laboratory technics, we have focussed on the rate of killing of M. leprae during initial therapy, neglecting those events that occur later in therapy, events that may be far more important in determining the success or failure of treatment. I'd like, then, to open the discussion with two questions. First, how can we best measure very small proportions (<1:1000) of viable M. leprae, and is it important to attempt to do this? Second, can we expect the use of combined treatment regimens to have an effect on the population of surviving drug-susceptible M. leprae?