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The rate of relapse in lepromatous leprosy following completion of twenty years of supervised sulphone therapy

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Summary In July 1970, 362 leprosy patients, all long-term residents of Sungei Buloh Leprosarium, who had been classified as lepromatous (LL and BL according to the Ridley–Jopling classification), and who had commenced treatment with sulphones as inpatients during the years 1948–1951, were 'released from control'. During a period of follow-up observation extending over 8–9 years, 25 of these patients relapsed clinically, giving an overall relapse rate of 8·6% and an average risk of relapse of 1·04 per 100 patient-years of observation. This risk did not change significantly from year to year during the period of observation. Of eight strains of *Mycobacterium leprae* isolated from patients in relapse, five were found to exhibit some level of dapsone resistance in mice. That the risk of relapse of lepromatous leprosy after long-term monotherapy with dapsone is so small is surprising, considering the deficient immune response to *M. leprae* characteristically displayed by these patients. Despite the small risk of relapse, it is recommended that smear-negative lepromatous patients who have received long-term monotherapy with dapsone receive a course of multidrug therapy before release from control.

Introduction

Early in the history of sulphone therapy, it was accepted that lepromatous

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patients whose treatment was interrupted subsequently relapsed.[1] Nevertheless, no assessment had been made of the risk of relapse following completion of long-term treatment of lepromatous leprosy, continued for many years after smear-negativity had been achieved. Therefore, when the decision was taken to stop the administration of dapsone to 362 lepromatous patients who had received well-supervised treatment for 18·5–21 years, we undertook to conduct a long-term follow-up. It proved possible to investigate a proportion of the patients who subsequently relapsed by histopathologic examination, and by assessing the susceptibility of their strains of *Mycobacterium leprae* to dapsone. This report presents the findings upon completion of an 8- to 9-year period of observation.

Materials and methods

In 1970, all surviving permanent residents of the Sungei Buloh Leprosarium (SBL) who had been admitted between 1929, the year of its founding, and the end of 1951 were reviewed. Patients were selected who: 1, had commenced sulphone treatment during the period 1948 (when sulphones had been introduced to SBL[2]) to the end of 1951; 2, were maintained on therapy with dapsone; 3, had been clinically inactive and smear-negative for at least 5 years; 4, were not known to be dapsone resistant; and 5, had received no antileprosy drugs other than dapsone, thiacetazone, thiambutosine and streptomycin. These patients had initially been treated with one of several sulphone regimens; the majority had received dapsone, 200 mg once or twice weekly by injection for the first two months, after which the dosage was increased gradually to 300–500 mg twice weekly, whereas some patients had been treated initially with solapsone (Sulphetrone^{R}) by injection in a twice-weekly dose of as much as 5 ml (1·5 g), and some with oral solapsone, 500–1000 g during the first year.[2] Between 1952 and 1963 or 1964, the majority had been maintained on dapsone, 300–400 mg twice weekly by injection for 10–12 months each year; almost every injection had been recorded.[3] After 1963 or 1964, most patients received supervised dapsone orally in a dosage of 200 mg twice weekly; a few continued treatment with parenteral dapsone.

A total of 362 lepromatous patients, whose treatment had been stopped in July 1970, met the enumerated criteria. One-third of these patients had completed 8 years, and two-thirds 9 years of follow-up at the time the records were assembled for this analysis.

These patients had been classified as lepromatous (LL and BL)[4] according to the following criteria: 1, their pretreatment classification, recorded in 1947–1952; 2, their current clinical classification; 3, their admission smears (or immediate pretreatment smears, for those admitted before 1947); and 4, the time required to become smear-negative, according to the results of the smears that were made annually on all residents of SBL.

Records of pretreatment classification and the results of smears were available

for almost all patients, and the results of serial smears were available for most. In general, patients classified as lepromatous had been classified before treatment as 'L' or 'N?L'. Clinically, they appeared to be patients with fully treated, quiescent LL or BL leprosy. Their pretreatment smears (routinely made from both ear lobes and one additional active skin site, and scored as negative, ±, 1+, 2+ or 3+[2]) were scored as 2+ or more at all 3 sites, suggesting LL, or those from one ear and the skin site were scored as 2+ and 3+, respectively, or both were 3+, with the other ear scored as negative or weakly positive, suggesting BL leprosy.

All of the patients were followed by means of an annual full clinical examination for leprosy. Smears were taken from those found at the time of an annual examination to have clinical evidence of relapse, or who presented between annual examinations with clinical evidence of relapse. Biopsies were taken from patients who consented to the procedure, one portion of tissue being fixed for histopathological examination and the other employed fresh for isolation of *M. leprae* and testing of dapsone susceptibility by inoculation of mice.[5] The diagnosis of relapse was based on clinical findings, supported by the results of smears from the relapse lesions.

For the purpose of this analysis, the risk of relapse was calculated as the number of relapses per 100 patient-years of observation. In calculating the number of man-years of observation, patients withdrawn from follow-up because of relapse, reinstitution of treatment, or death were considered to have been withdrawn from the study in the middle of the year in which these events occurred (*i.e.* the number of man-years of observation during any year was taken as the average of the number of patients at risk of relapse at the beginning of the year and the number remaining at risk at the end of the year). Patients who were still under observation were finally assessed during the 8th or 9th year of follow-up and appear under 'Withdrawn from observation' in Table 1.

Results

The outcome of the 362 lepromatous patients studied is presented in Table 2. Twenty-five patients relapsed; 29, who were uneasy without treatment after so many years of therapy, or who were friends of patients who relapsed, insisted upon resuming dapsone treatment; 3 of these patients died during the period of follow-up, and none relapsed. Sixty-eight of the remaining patients died from intercurrent disease during follow-up.

Relapse occurred during each year of follow-up, as shown in Table 1; the risk of relapse did not vary significantly from year to year during the 8 to 9 years of observation. The cumulative rate of relapse was 1·04 per 100 patient-years of observation.

Eight of the patients who relapsed were female (32%), as were 141 (39%) of the 362 patients studied. Twenty-two of the patients who relapsed were Chinese, 3

Table 1. Sungei Buloh Leprosarium 'Release from Control' (July 1970) Lepromatous Patients—Annual incidence of relapse and other outcome during the nine-year follow-up period.

Year of follow-up	Number of patients under observation at beginning of year	Relapsed	Died	Withdrawn from observation	Patient-years of observation	Relapse rate (per 100 patient-years)
1	362	2	8	13	350·5	0·6
2	339	3	8	2	332·5	0·9
3	326	2	14	5	315·5	0·6
4	305	4	9	0	298·5	1·3
5	292	6	8	1	284·5	2·1
6	277	3	6	2	271·5	1·1
7	266	2	7	0	261·5	0·8
8	257	2	10	73*	214·5	0·8
9	172		1	1 170*	86	0·6
Total		25	71*	266	2415	
mean						1·04

* Patients analysed after 8th and 9th years of follow-up (see text).

Table 2. Sungei Buloh Leprosarium (SBL) 'Release from Control' Lepromatous Patients—Outcome at end of follow-up period.

Outcome	Number of patients for each outcome according to treatment status		
	Patients who remained off treatment	Patients who without relapsing insisted on going back onto treatment	Total
Relapsed	25	0	25
Under SBL treatment	0	24	24
In SBL, not under treatment	222	2*	224
Died	68	3	71
Discharged (not under treatment)	18	0	18
Total	333	29	362

* Two patients insisted on returning onto dapsone treatment, but then stopped for the second time.

were Indian, and none was Malay, yielding proportions that did not vary significantly from those in the entire group of patients studied. Twenty-one of the patients who subsequently relapsed had been treated initially with dapsone by injection, and 4 with solapsone. One patient initially treated with dapsone, and another with solapsone had also been treated with thiacetazone.

Most of the relapses presented clinically as a small number of asymmetric lepromatous (LL or BL) lesions, showing various degrees of activity; the clinical presentations were not dissimilar from those of relapses with dapsone resistance during dapsone monotherapy. One patient (No. 5077) developed several annular BT lesions,[6] although he had been classified as advanced lepromatous (LL_s)[7] leprosy in 1948. In the cases of those patients who underwent biopsy, histopathological examination fully supported the clinical evidence of activity. The bacteriological index of smears made from the relapse lesions varied widely from patient to patient, ranging from 0 to 5 on Ridley's logarithmic scale.[8] The morphological index (MI) varied from 0 to 33%; in general, more active lesions were associated with higher values of the MI.

Ten of the 25 patients who relapsed agreed to undergo biopsy in the Leprosy Research Unit. The susceptibility to dapsone of 7 of the strains was subsequently assessed; 3 proved to be fully susceptible, 2 were resistant at the lowest level (the organisms multiplied in mice administered 0·0001% dapsone in the diet), 1 was of intermediate resistance (multiplication occurred in mice fed 0·001% dapsone in the diet), and 1 strain was fully resistant (the organisms multiplied in the mice fed

Table 3. Clinical, histological and bacteriological findings, and their dapsone sensitivity in mice of nine lepromatous patients subjected to biopsy on relapse following 'release from control' after 19–22 years of sulphone therapy.

Patient number	Initial treatment	Year of relapse	Classification		Smears		Dapsone sensitivity of *M. leprae* in mice
			Clinical	Histological	Bacterial index	Morphological index	
10614	Solapsone	1	BL	BL	2·7	27	0·01% dapsone
6281	Inj. dapsone	3	LLs	LLs	3·0	2	NT*
10853	Inj. dapsone	4	LLs	LLs	3·1	2	Sensitive
9534	Inj. dapsone	4	LLs	BL	1·9	15	Sensitive
10027	Inj. dapsone	4	LLs	BL	1·7	0	0·0001% dapsone
8660	Inj. dapsone	4	LLs	LLs	4·0	1	0·001% dapsone
5077	Inj. dapsone	5	LLs/BT	BT	0·3	0	0·01% dapsone†
6466	Inj. dapsone	7	LLs	LLs	2·0	26	Sensitive
6978	Inj. dapsone	9	LLs	LLs	3·5	5	0·0001% dapsone

*NT = No multiplication of *M. leprae* in control mice.

† This strain of *M. leprae* was eventually isolated in 1979 and found to be resistant to 0·01% dapsone in the mouse diet.

0·01% dapsone). An additional strain (that from patient No. 5077), isolated 4 years after relapse, was also found to be fully resistant (see Table 3).

Discussion

In 1947, following his introduction of sulphones to the chemotherapy of leprosy,[9] Faget reported[10] the achievement of negative skin smears in some treated lepromatous patients. By that time, he had already learned that a smear-positive patient who stopped treatment could relapse, although the relapse sometimes occurred only after many months or years.[1] For this reason, he adopted a policy of continuing treatment for a full 12 months after the patient achieved smear-negativity. In that same year, Muir suggested[11] a similar policy, *i.e* that treatment should be continued at least until the patient had remained smear-negative for a period of 6–24 months, depending upon the severity of disease at the beginning of treatment, and upon the duration of treatment required to produce the first negative smears.

Those of Faget's patients whose smear-results are presented in the publication[10] became smear-negative after 0·5–5 years of treatment; in retrospect, therefore, the majority may be considered to have suffered from borderline-lepromatous (BL) or mild (L_1) lepromatous leprosy. (The majority of the patients in the present study suffered from moderately advanced or advanced lepromatous or BL leprosy.) Nevertheless, Erickson reported[12] that the outcomes of these patients were disappointing. Five of 11 lepromatous patients whose treatment had been stopped became smear-positive again after 0·5–3 years, of whom three showed clinical as well as bacteriological evidence of relapse, whereas none of 22 similar patients who continued treatment after becoming smear-negative showed clinical evidence of relapse, and only 1 exhibited mild bacteriological relapse 6 months after becoming smear-negative. (The possibility that sampling error might have accounted for this bacteriological relapse was not discussed.) The difference of relapse rates, 24·4 per 100 patient-years among those stopping treatment, to be compared with 1·7 per 100 patient-years among those continuing treatment, was striking. The patients who relapsed responded well to resumption of treatment. Erickson therefore recommended[12] that treatment of lepromatous patients should be continued indefinitely, although the dosage might safely be reduced once the patients had become smear-negative. His advice was accepted by Chaussinand,[13] at least for patients with advanced lepromatous leprosy, whose smears were still positive after 4–5 years of treatment.

Larger series from Africa failed to confirm Erickson's disappointing results. In 1954, Lowe reported[14] that, in a follow-up of 139 lepromatous patients, the majority of whom did not have severe involvement, who were treated with sulphones for 24–82 (mean 41) months, there were minimal clinical signs of relapse (neuritis) in only 2. Thirteen others showed only minimal bacteriological

evidence of relapse, and none exhibited both bacteriological and clinical evidence. The bacteriological findings were of doubtful significance: 5 of 6 smear-positive patients, who remained untreated, later became smear-negative again. It is difficult to interpret Lowe's findings, because, although all of the relapses occurred within the first 2 years without treatment, the mean duration of follow-up was only 22 months, and was in no case longer than 61 months. Both Davey, reporting in 1958,[15] and Browne in 1966,[16] confirmed that relapse was rare among discharged lepromatous patients, Davey stating that the relapse rate was 2·3% in 'unequivocal lepromatous cases', and higher in borderline leprosy patients.

Few other series have been published. The two best known, those of Rodriguez[17] and Quagliatto *et al.*,[18] were based only on bacteriological findings, and the majority of their patients were on continuing, if often irregular, treatment. Nevertheless, the general experience was that lepromatous patients frequently relapsed upon cessation of treatment.[19] In 1966, therefore, the World Health Organization recommended[20] that lepromatous patients becoming clinically inactive and smear-negative should be continued on full treatment for 5 years before they were 'released from control'. In 1970, influenced largely by the results of Quagliatto *et al.*,[18] the WHO recommended continuing treatment for at least 10 years.[21]

The decision, by Dr M K Bhojwani, as Director of the National Leprosy Control Centre, Sungei Buloh, to carry out the recommendation made by the WHO Expert Committee on Leprosy at its third meeting,[20] by releasing from control (*i.e.* stopping treatment of) a large group of long-treated and smear-negative lepromatous patients, provided a unique opportunity to observe the subsequent rate of relapse. Follow-up was greatly facilitated because the patients had made their homes in the SBL in the days of long-term segregation, and only 18 of the 362 moved away during the 8- to 9-year period of observation. In addition, because of their fear of leprosy, and because they had much earlier been provided with permanent homes in the SBL, the patients had no incentive to take treatment irregularly. Moreover, during the period 1948–1963, during which a majority of the patients received dapsone twice weekly by injection, irregular attenders had been quickly noted and reprimanded. Thus, these patients had, as a group, received unusually regular and well-documented treatment.

Although a word of caution appears to be in order, the significance of our findings is clear. A relapse rate of 1·04 per 100 patient-years of observation among patients with advanced lepromatous leprosy, who had been treated for about 20 years with regularly administered dapsone as monotherapy is considerably smaller than that expected, considering the persisting inability of such patients to mount an effective immune response to *M. leprae*. Of course, these results were obtained from a group of patients who had received exceptionally regular, well supervised treatment, the majority commencing treatment with dapsone in full dosage. The patients were among the first to receive dapsone in Malaysia, and therefore primary dapsone resistance was then nonexistent. Moreover, a number

of their peers had already relapsed while on treatment from the development of dapsone resistance before the institution of release from control, and had been changed to alternative treatment.[3,22] One should perhaps not expect so low a rate of relapse among similar patients whose treatment was administered in the context of the average leprosy control programme. On the other hand, the risk of relapse after release from control might well be smaller among patients who had received a course of multidrug therapy according to the recommendations of the WHO Study Group on Chemotherapy of Leprosy for Control Programmes.[23] In fact, the results of this study encourage the belief that a course of finite duration of a chemotherapeutic regimen more effective than dapsone monotherapy, especially a regimen including rifampicin, might suffice to prevent relapse in the great majority of lepromatous patients, and make achievable the goal of control of leprosy.

A final consideration is the desirability of administering an end-phase of multidrug therapy to the smear-negative patients who have been treated only with sulphones; such patients are well known to nearly all leprosy control programmes. We recommend that such patients, many of whom may have been irregularly treated in the past, should be administered a multidrug regimen for some period prior to their release from control. As the present study has demonstrated, these patients are at some risk of relapse; and some of the relapses are likely to be associated with the emergence of dapsone-resistant *M. leprae*. This has, in fact, been attempted in the Malta trial, with virtual freedom from relapse.[24]

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