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Relapse Rates in Lepromatous Leprosy According to Treatment Regularity[1]

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Patients with lepromatous leprosy may now hope for a limited period of treatment instead of life-long therapy ([14]). The study of relapses after skin smears become "negative for *Mycobacterium leprae*" will help determine the optimal duration of treatment. We therefore continued our previous analysis of relapses among smear-negative lepromatous (LL) and borderline lepromatous (BL) patients on dapsone (DDS) monotherapy ([2]) to find out whether continued treatment during smear negativity has as much influence on relapse rates as previous treatment during smear positivity.

Much data is available on the magnitude of relapse rates among treated "multibacillary" leprosy patients ([4, 6–13]), including that from our own previous report ([2]). However, none of these studies considered the regularity of treatment during smear positivity separately from that during smear negativity.

MATERIALS AND METHODS

The well-documented leprosy control program of the Schieffelin Leprosy Research and Training Centre (SLR&TC), Karigiri, India, among the 450,000 inhabitants of Gudiyatham Taluk in South India, has previously been described in detail ([1]). The most relevant points alone are repeated here. The whole population in the area is regularly examined for leprosy. All known patients are registered for treatment, which they collect at monthly village clinics near their homes. Details on each patient are carefully maintained in an individual patient record.

All 1580 LL and BL patients residing in Gudiyatham Taluk (area = 1320 km^2) were listed on 31 December 1977 from the treatment register of SLR&TC, Karigiri. Data were assembled for each patient, from the date of registration up to 28 February 1981, from individual patient records; 157 of 1580 patients had insufficient data. Of the remaining 1423 patients (90.1%), all were included who had been smear positive and had had at least two consecutive negative skin smears at any time after registration; 1008 patients satisfied these criteria.

DDS monotherapy was used throughout the study period, and smear-negative patients continued on treatment. Smears were taken annually from a minimum of four skin sites: earlobe and chin on the right, forehead and buttock or thigh on the left.

"Relapse" is taken to mean the re-appearance of *M. leprae* in the skin smears of a smear-negative patient, excluding those cases where a single bacillus was found at only one skin site on an isolated occasion. The "period of smear negativity" for a patient is defined as the single longest period after registration which started with, ended with, and included only negative skin smears. The sum of the periods of smear negativity for a group of patients yields their "person-years of smear negativity." "Regularity of treatment" during a stated period is defined as the percentage of months throughout the period during which the patient attended a monthly village clinic to collect tablets. Those who collected fewer tablets were assumed to have ingested fewer tablets, on the average, than those who collected tablets regularly. In the interest of clarity, it was decided before analysis that treatment regularity during smear negativ-

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ity should not have class intervals identical to those for regularity during smear positivity.

"DDS-resistant infection" ([1]) had been diagnosed among patients whose annual skin smears showed a continuing increase in the number of bacilli, despite >50% regular treatment overall. Some patients with enough bacilli [bacterial index (BI) ≥ 2+] for successful inoculation of the mouse foot pad were also tested for the presence of DDS-resistant bacilli ([3]).

The chi-squared test with correction for continuity was used to determine the statistical significance of observed differences.

RESULTS

The lowest relapse rate during the initial three years of smear negativity was found among the patients with the better treatment regularities during both past smear positivity and smear negativity (The Table). For example, until the third year of follow up, patients with a history of less regular (≤66.7%) treatment during past smear positivity had 4.9% relapses per year (17 + 11 = 28 relapses during 279 + 288 = 567 person-years of smear negativity); whereas those with more regular (>66.7%) treatment had only 2.8% relapses per year (26 relapses during 946 person-years). The difference is statistically significant ($p < 0.05$).

A striking finding, however, is that from the fourth year of follow up onward, patients treated more regularly during past smear positivity did not have lower relapse rates than those treated less regularly. On the other hand, more regular (>75%) treatment during smear negativity was consistently accompanied by lower relapse rates than less regular (≤75%) treatment even seven or more years after the attainment of smear negativity (The Figure).

Patients with >75% regular treatment from the seventh year of smear negativity (The Table) had 1919 (551 + 1378) person-years of observation. Twenty patients relapsed, giving a relapse rate of 1.0% per year; 16 of these patients eventually became smear negative again while continuing on DDS monotherapy. Two of the remaining patients were demonstrated to harbor DDS-resistant bacilli by the mouse foot pad test ([1, 3]); one of whom showed a continuing increase in bacilli in successive skin smears and, hence, was diagnosed to have DDS-resistant infection ([1]).

THE TABLE. *Relapses among smear-negative LL and BL patients by regularity of treatment during smear negativity and regularity of treatment during smear positivity.*

Duration of smear negativity (yrs)	Treatment regularity during smear negativity	Treatment regularity during smear positivity[a] ≤66.7%	>66.7%
1–3	≤75%	17/279 (6.1%)	9/191 (4.7%)
	>75%	11/288 (3.8%)	17/755 (2.3%)
4–6	≤75%	10/209 (4.8%)	6/123 (4.9%)
	>75%	1/206 (0.5%)[b]	9/521 (1.7%)
≥7	≤75%	13/557 (2.3%)	8/297 (2.7%)
	>75%	4/551 (0.7%)	16/1378 (1.2%)

[a] Number of patients relapsed/person-years smear negativity.

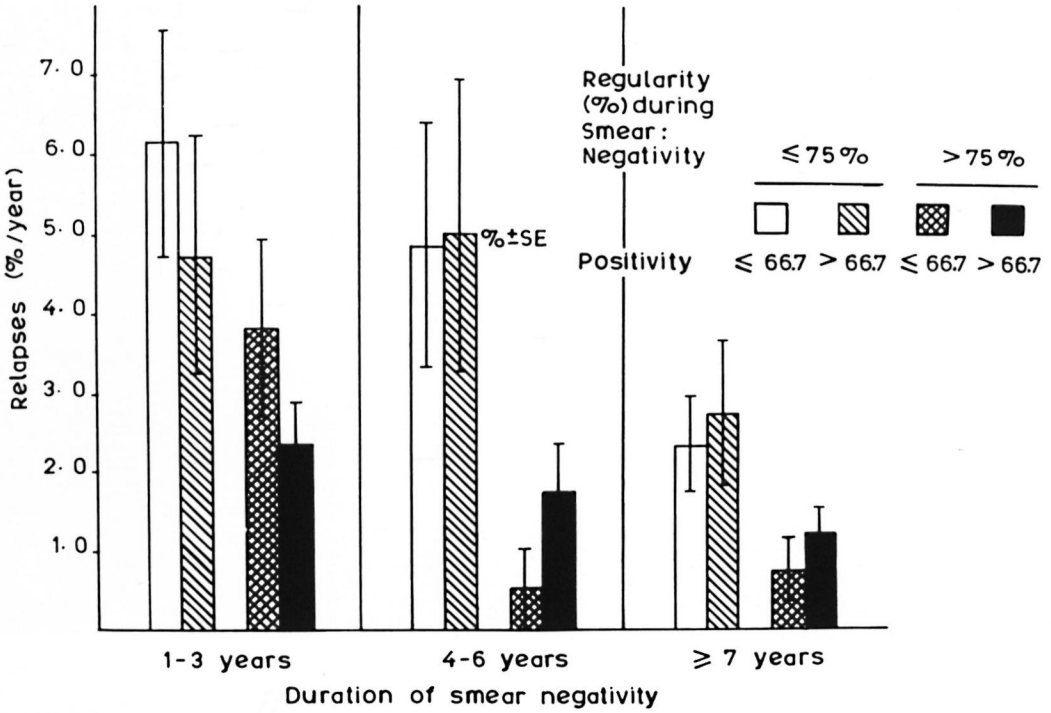
[b] Significantly less than ≤75% treatment regularity during 4–6 years of smear negativity; $p < 0.005$, chi-squared test.

DISCUSSION

"Relapses" in lepromatous leprosy can occur due to "endogenous" *M. leprae* from within the patient, or "exogenous" *M. leprae* from external sources, or both. During the initial three-year period of follow up, more regular treatment during past smear positivity was associated with lower relapse rates. Perhaps inadequately treated *M. leprae* resume multiplication and manifest as a relapse within this initial period of smear negativity. Beyond this period, relapse rates are no lower for the patients treated more regularly in the past than for those with less regular past treatment.

Relatively regular treatment during smear positivity seems to have no salutary effect on the risk of relapse after the third year of smear negativity. Perhaps this is because "endogenous" *M. leprae* (from within the patient) do not pose as great a threat as "exogenous" bacilli after the third year of smear negativity.

Beyond the initial period of smear negativity, the risk of "endogenous" *M. leprae* multiplying should tail off, and relapse rates similarly tail off, unless "exogenous" sources of *M. leprae* (outside the patient) are avail-



THE FIGURE. Relapses among smear-negative LL and BL patients by regularity of treatment during smear negativity and smear positivity.

able. In the one non-endemic area where treatment was stopped after using four drugs for a period ([7]), none of 80 LL and BL patients with negative smears had relapsed. The risk of relapse from "endogenous" *M. leprae* may have been minimized in that study by the use of four drugs. However, the low (possibly zero) relapse rates are consistent with the view that few "exogenous" *M. leprae* were available in that non-endemic area.

The frequency with which "exogenous" sources of *M. leprae* may lead to detectable bacilli in the skin of an individual was partly measured by a total population study of apparently noninfected persons in a leprosy-endemic area ([5]); 5.8% of about 7000 persons with no sign of leprosy were found to harbor acid-fast bacilli in the skin of one earlobe. The corresponding figure among patients with apparently "resolved" leprosy was 13.33%. That these bacilli were *M. leprae* was suggested not only by their failure to grow on routine mycobacterial media but, more strongly, by the higher-than-average incidence of subsequent clinical leprosy among the apparently noninfected persons harboring the bacilli.

One interesting group in the present study is the 20 patients who "relapsed" after having been smear negative for seven or more years, despite >75% regular treatment during smear negativity (The Table). Although bacilli reappeared in their skin smears, 16 of them went on to become smear negative again while on DDS monotherapy. DDS-resistant infection, therefore, seems an unlikely explanation of their transient smear positivity. If "endogenous" *M. leprae* had multiplied to give the positive smears, those patients treated more regularly during past smear positivity should have a lower "relapse" rate than those less regularly treated. Instead, their relapse rate is at least as high: 1.2% per year for those with more regular (>66.7%) treatment during smear positivity compared to 0.7% per year for those with less regular (≤66.7%) treatment. This is consistent with the explanation that the bacilli could have come from "exogenous" sources and were, therefore, unaffected by previous treatment during smear positivity.

The rarity of DDS-resistant infection, or even of sufficient bacilli to inoculate the mouse foot pad, among the patients who "relapsed" after years of smear negativity is in keeping with our earlier studies ([1]). We had found that smear negativity indicated a significantly reduced risk of DDS-resistant infection.

SUMMARY

In Gudiyatham Taluk, South India, 1008 lepromatous (LL) and borderline lepromatous (BL) patients were studied. They had previously been smear positive, had attained smear negativity, and continued on DDS monotherapy. "Relapse" was defined as the reappearance of *Mycobacterium leprae* in skin smears. The area is endemic for leprosy.

The lower relapse rates in the first three years of smear negativity alone were associated with more-regular treatment during both past smear positivity and smear negativity. From the fourth year of smear negativity onward, only the more-regular treatment during smear negativity was associated with lower relapse rates; whereas patients with more-regular treatment during past smear positivity had no lower risk of relapse than those with less-regular treatment.

The finding that regularity of treatment during smear positivity seems to have no effect on relapse rates beyond the third year of smear negativity is discussed. In a leprosy-endemic area, it is argued that beyond the first three years of smear negativity in an LL or BL patient, sources of *M. leprae* outside the patient may be more responsible for relapse than the patient's own bacilli.

RESUMEN

Se estudiaron 1008 pacientes lepromatosos (LL) y lepromatosos intermedios (BL) en Gudiyatham Taluk, al sur de la India. Los pacientes que previamente habían sido baciloscópicamente positivos, alcanzaron la negatividad baciloscópica y continuaron con monoterapia a base de dapsona (DDS). Se consideró que hubieron recaídas cuando reaparecieron bacilos en los extendidos de linfa cutánea. En el área estudiada la lepra es endémica.

Las bajas frecuencias de recaída en los primeros 3 años de negatividad baciloscópica se pudieron asociar con un tratamiento muy regular tanto durante la positividad baciloscópica previa como durante la etapa de negatividad. A partir del cuarto año de negatividad, las bajas frecuencias de recaída sólo se pudieron asociar con un tratamiento muy regular durante la etapa de negatividad baciloscópica. Los pacientes con un tratamiento muy regular durante la positividad baciloscópica previa tuvieron igual riesgo de recaída que aquellos pacientes con tratamiento menos regular.

La regularidad del tratamiento durante la positividad baciloscópica no parece tener efecto sobre la frecuencia de recaídas después del tercer año de negatividad. Se argumenta que en un área con lepra endémica, las fuentes de *Mycobacterium leprae* externas son más importantes que los bacilos del propio individuo como causa de recaída en un paciente LL o BL después del tercer año de negatividad baciloscópica.

RÉSUMÉ

On a étudié 1008 malades lépromateux (LL) et lépromateux dimorphes (BL), dans le Gudiyatham Taluk, en Inde du Sud. Ces malades avaient été antérieurement bactériologiquement positifs; ils étaient négatifs au frottis cutané, ils étaient toujours sous monothérapie par la DDS. Les "récidives" ont été définies comme la réapparition de *Mycobacterium leprae* dans les frottis cutanés. Cette région est endémique pour la lèpre.

Un taux réduit de récidives au cours des trois premières années à bactériologie négative était associé avec un traitement plus régulier avant la négativation, tant au cours de la période précédente de bactériologie positive, qu'au cours de la période caractérisée par une bactériologie négative. A partir de la quatrième année à bactériologie négative, et au cours des années suivantes, l'abaissement du taux de récidive n'était associée qu'avec un traitement plus régulier au cours de la période négative. Les malades ayant poursuivi leur traitement de manière plus régulière au cours de la période à bactériologie positive, ne présentaient pas un taux de récidive plus faible que ceux qui avaient eu un traitement moins régulier au cours de cette période.

On discute cette observation que tend à montrer que la régularité du traitement au cours de la période de bactériologie positive semble n'avoir aucun effet sur les taux de récidives au-delà de la troisième année de bactériologie négative. Dans une région endémique pour la lèpre, on peut défendre l'hypothèse qu'au-delà des trois premières années de bactériologie négative chez des malades LL ou BL, les sources de *M. leprae* extérieures au malade peuvent être davantage responsables pour les récidives que les bacilles du malade lui-même.

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