

RELAPSES IN LEPROSY<sup>1</sup>

UZUAKOLI SETTLEMENT, 1958-1964

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This report deals with leprosy patients who had been treated in the Research Unit, Uzuakoli Leprosy Settlement, and who, having relapsed during the seven-year period 1958-1964 (inclusive), were readmitted to the Settlement. It thus follows directly on the report submitted by Davey (<sup>1</sup>) at the Tokyo Congress, in which the following figures were given: during the years 1949-57, there were 36 cases of relapse out of 631 patients discharged, 27 occurring within 2 years of discharge; the relapse rate among patients with lepromatous leprosy was 2.3 per cent; borderline, 29 per cent; tuberculoid, 6 per cent; and indeterminate, "common." After dapsone therapy, 4 per cent of patients relapsed; after thiacetazone, 22 per cent; after dapsone and thiacetazone alternately, 3 per cent. Puberty, lactation and malnutrition occurred with significant frequency among patients who relapsed.

In an unpublished report from the neighboring Oji River Settlement dealing with the same period, Garrett (<sup>2</sup>) gives the following figures: there were 51 relapses out of a total of 636 discharges; no relapses among 15 patients with lepromatous leprosy, 31 out of 189 with borderline, 17 out of 415 with tuberculoid, and 3 out of 17 with indeterminate leprosy. In the borderline group, the relapse rate was 5 out of 6 after one year's treatment with dapsone, 16 out of 54 after 2 years', 8 out of 71 after 3 years', one out of 34 after 4 years', and one out of 24 after 5 years' treatment.

During the period 1958-1964 patients discharged symptom-free numbered 920 from Uzuakoli Settlement itself, and 4,636 from the District Clinics. During the same period, 51 relapsed patients were admitted to the Settlement, and 293 to the District Clinics. Although the figures are not strictly comparable, since the populations discharged are not identical with the populations from which all cases of relapse came, the approximate percentage of relapsed patients among all patients discharged over this period is 5.5 for the Settlement and 6.3 for the District Clinics.

Since the data with respect to patients readmitted for treatment to District Clinics are in some cases incomplete, and since furthermore the patients were not personally examined by the writer, they will be excluded from further consideration in this paper.

*Age distribution.*—With such small numbers, no conclusions can be drawn regarding the age distribution of relapsed patients, except that it probably does not differ materially from that of all patients

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diagnosed at the Diagnostic Clinic, Uzuakoli, 1959-64. The relation of relapse and the age when treatment was started is indicated in Table 1.

TABLE 1.—*Relapse in relation to age at first treatment.*

Age when first treated for leprosy	Patients who eventually relapsed		All patients diagnosed	
	Number	%	Number	%
0 - 9 years	1	2	31	3.1
10 - 19 "	7	14	155	15.3
20 - 29 "	10	20	148	14.6
30 - 39 "	12	24	282	27.8
40 - 49 "	18	35	192	18.9
50 - 59 "	3	6	120	11.8
over 60 "	—	—	87	8.6
	51		1,015	

*Classification of relapsed cases.*—The original (and necessarily tentative) classification of these patients compared with the proportions of different types of leprosy in all patients diagnosed at the Diagnostic Clinic during the period 1959-64, is summarized in Table 2.

TABLE 2.—*Classification of patients with relapse.*

Original diagnosis	Relapsed patients		All cases diagnosed	
	Number	%	Number	%
Lepromatous	14	27	145	14.3
Borderline	22	43	153	15.1
Tuberculoid	6	12	673	66.3
Indeterminate	9	18	44	4.3
	51		1,015	

While the criteria for the differentiation of the polar types of leprosy have remained fairly constant over the period from which the relapsed patients were drawn, the nomenclature used in the case sheets of the wide variety of intermediate forms encountered provides evidence of the clinician's difficulties. Analysis on the basis of the four main types does not distinguish the patients with typical leprosy from those with atypical features that were eventually to prove significant in determining liability to relapse.

Ten of the 51 patients had frank lepromatous leprosy, and the relapses were frankly lepromatous. Only 2 originally had typical tuberculoid leprosy, and in them the relapse was characterized by atypical features. Two had "low-resistance tuberculoid leprosy" sometimes called "bacteriologically negative dimorphous macular leprosy," and in them lesions similar to the initial lesions appeared on relapse; old lesions became active and showed a tendency to centrifugal extension.

The leprosy lesions in 22 patients were originally classified as of the borderline variety. This figure, however, should be augmented by 15, which represents the number of patients in whom it is evident that the original diagnosis of indeterminate leprosy (9 patients), lepromatous (4 patients) or tuberculoid (2 patients) did not take sufficient cognizance of the atypical features described in the records. The diagnosis was evidently a convenient label, the best and shortest and most adequate available. It is apparent that an overwhelming proportion of patients in this series manifested forms of leprosy difficult to classify by reason of the atypical nature of the skin lesions.

*Signs of relapse.*—The commonest sign of relapse was either a reactivation of preexisting but quiescent lesions, or the sudden appearance of new lesions, perhaps in great numbers.

The new lesions might be of similar appearance to the former existing lesions when the latter had been active, or might arise in crops showing features of acute exacerbation, i.e., centrally raised or plaque-like elevations, reddish or pinkish, and rapidly increasing in extent and elevation. Successive crops of such lesions might be at different stages of development in the same patient, i.e., active and extending, or stationary and becoming less active, retrogressing, or quiescent, and the pigmentary changes showed a wide range from red to dull yellow-brown.

A most serious aspect of relapse, not unexpected in view of the high proportion of borderline cases in the series, was the number of patients whose clinical relapse was heralded or accompanied by signs of serious neuritis in one nerve trunk, or more commonly in several, perhaps in all, of the main trunks of the limbs. This was usually either an exacerbation or a recurrence of a preexisting neuritis. Nerve damage on relapse was classified as: slight in 10 patients, moderate in 12, and severe in 10; in addition, 3 patients developed acute neuropathic ulceration. In 16 there was no clinical evidence of nerve damage.

*Histologic examination.*—Sections of skin of some of these 51 patients are available. They serve to confirm the clinical findings and the inferences drawn therefrom. Had it been possible to remove typical portions of typical lesions at various stages during treatment, a convincing confirmation of the clinical suspicions would have been available for subsequent study.

*Bacteriology.*—Table 3 summarizes the bacterial index (maximum: 4.0) calculated as the average of that found in skin smears obtained usually from 8 sites (skin 4, ear lobes 2, nasal mucosa 2).

The majority of the 21 patients with bacteriologically negative smears were classified clinically as suffering from either borderline or indeterminate leprosy. Routine bacterioscopy of material obtained from several sites at successive reexaminations after discharge symptom-free, often confirms clinical suspicion of relapse. Bacterial positivity may be a surprise finding, preceding clinically appreciable exacerbation; it is sometimes much greater than the clinical state

would suggest. Four patients whose skin smears on admission and subsequently had been completely negative, were found to have highly positive smears at all sites on relapse. The importance of routine bacterioscopy on regular follow-up examinations cannot be overstressed.

TABLE 3.—*Bacterial index of relapsed patients.*

B.I.	Number of patients
0	21
0.1 - 0.9	13
1.0 - 1.9	8
2.0 - 2.9	5
3.0 - 4.0	4
	51

*Drugs used.*—In this series, no special drug or regimen can be singled out as having been used in an unusually large proportion of patients who relapsed. Table 4 indicates the drugs used.

These figures reflect the proportions of patients during the period under consideration who were placed in these various treatment groups.

As a matter of historic interest, the patients (5 lepromatous, and 5 borderline) treated with hydnocarpus oil, were under treatment on an average for nearly 6 years and relapsed after an average remission of 12½ years.

TABLE 4.—*Drugs used in relapsed patients.*

Drugs	Number of patients
Dapsone alone	27
“ and thiambutosine	3
“ “ thiacetazone	1
“ “ ditophal	1
“ “ hydnocarpus oil	3
Diaminodiphenyl sulfoxide	4
Thiambutosine	3
Thiacetazone	2
Hydnocarpus oil	7
	51

*Length of treatment before relapse.*—In the early days treatment tended to err on the short side, especially in patients whose lesions appeared to respond satisfactorily, with repigmentation and rapid elimination of fragmented *M. leprae*; that is precisely the kind of leprosy that does relapse. Treatment was given for less than 3 years in 19 patients; less than 4 in 8; less than 5 in 10, less than 6 in 4, and for 6 years or longer in 10.

Half the patients suffering from apparently benign forms of lep-

rosy, and whose skin smears (from the lesions themselves, the ear lobes and the nasal mucosa) were bacteriologically negative on admission, received treatment for less than 3 years, and only 6 for longer than 4 years.

*Duration of remission.*—Fourteen patients relapsed within a year of discharge, 5 within 2 years, and 3 within 3 years. Thirty-three relapsed with 5 years of cessation of treatment; 9 in from 6 to 9 years, and 9 after 10 or more years.

*Regularity of relapsed patients at follow-up examination after discharge.*—All patients on discharge from Uzuakoli Settlement are advised to return regularly for clinical and bacteriologic examination, quarterly for the first year, then every 6 months for 2 years, and then annually.

In only 14 patients (out of 47 whose records are adequate in this respect) was attendance for reexamination classified as "good" or "excellent;" in 21 it was "poor" or "very poor," and in 12 it was "fair." In most cases, it is debatable if regular attendance could have revealed relapse at a much earlier date than when the patient actually attended for reexamination. Some patients failed to notice the reappearance of active lesions, or, having noticed them, failed to appreciate their significance and gravity. The relapse in 11 of the 51, unsuspected by the patient himself, was recognized during routine reexamination.

*Response to treatment after relapse.*—In most cases, the response to treatment was good but slow. In determining the length of treatment necessary after relapse, the tendency was to err on the side of caution, in view of both the history of over-optimistic discharge and subsequent relapse, and of the presence of acute or subacute polyneuritis.

#### DISCUSSION

In the great majority of patients in this series, no adequate immediate cause for the relapse could be found or was suspected. Pregnancy may have been the cause in 2 cases, and one patient asserted that his relapse followed a prolonged and severe "fever," perhaps typhoid. In this series, the influence of other presumably hormonal factors, such as puberty and the menopause, was not apparent.

Lepromatous leprosy on the whole is adequately treated, and regular bacteriologic examination ensures that treatment is continued for a sufficient time.

Patients with typical active tuberculoid leprosy who are considered to require treatment have an excellent chance of permanent arrest of disease. The course of treatment for them is more than adequate, and the risk of relapse very small.

Forms of leprosy diagnosed originally as "borderline," "indeterminate," "tuberculoid with borderline features" or "lepromatous with borderline features," are the kinds most likely to relapse. The

signs that should make for caution are: early and widespread nerve involvement, multiple lesions, lesions whose maximal elevation is central rather than peripheral, numerous daughter lesions, successive crops of lesions, minimal sensory loss in the lesions, slightly positive or variably positive lepromin test.

The obvious conclusion to be drawn is that the duration of treatment of the patients with borderline leprosy was inadequate. Possibly the significance and potential seriousness of the unstable and unpredictably variable kind of leprosy usually called borderline, were not sufficiently appreciated until the late 1950's.

Since such patients have been treated for a longer period, i.e., for at least 2 years after all signs of clinical activity have ceased, or (in the case of the bacteriologically positive lesions) for 2 years after the smears from all sites have ceased to show even fragmented bacilli or acid-fast dust, the number of relapses is becoming somewhat less frequent.

#### SUMMARY

During 1958-64, 51 patients who had been discharged symptom-free (representing about 6 per cent) were readmitted for treatment to the Uzuakoli Settlement because of relapse.

The original classification in these patients was: lepromatous 14; borderline 22; tuberculoid 6; indeterminate 9. According to the clinical descriptions, however, the lesions in 4 patients with lepromatous leprosy, 2 with tuberculoid and 9 with indeterminate disease, showed atypical features that brought them into the borderline group. Bacteriologic and histologic examinations afforded close correlation with clinical findings.

Treatment with no one drug or combination of drugs seemed especially liable to be followed by relapse. The length of treatment was short by modern standards.

Fourteen patients relapsed within a year of discharge, and another 8 within the next 2 years.

Only 14 patients were regular in the follow-up examinations after discharge.

Apart from the cutaneous evidence of relapse (appearance of new lesions or reactivation of old ones), the most serious feature of the relapse was the predominance of extensive and severe polyneuritis.

The response to treatment on readmission was on the whole satisfactory, but slow.

The commonest suspected cause of relapse was insufficient treatment in a patient predisposed to relapse because he was suffering from borderline leprosy, or leprosy showing atypical features.

#### RESUMEN

Durante 1958-1964, 51 pacientes que habian sido descargados libres de sintomas (representando alrededor del 6 por ciento) fueron readmitidos para tratamiento por recaída en el establecimiento Uzuakoli.

La clasificación original en estos pacientes fué: lepromatosos 14; límite (borderline) 22; tuberculoide 6; indeterminados 9. Sin embargo, de acuerdo a las descripciones clínicas, las lesiones en 4 pacientes con lepra lepromatosa, 2 con tuberculoide y 9 con enfermedad indeterminada, mostraron aspectos atípicos que los trajeron dentro del grupo límite (borderline). Los exámenes bacteriológicos e histológicos dieron una correlación estrecha con los hallazgos clínicos.

Los tratamientos no con una droga o combinación de drogas, parecieron especialmente capaces de ser seguidos por recaídas. La duración del tratamiento fué corto para los modelos modernos.

Catorce pacientes recayeron dentro del año de descarga, y otros 8 dentro de los 2 años.

Solamente 14 pacientes fueron regulares en los exámenes evolutivos después de la descarga.

Aparte de la evidencia cutánea de la recaída (aparición de nuevas lesiones o reactivación de las antiguas), el aspecto mas serio de la recaída fué la predominancia de la extendida y severa polineuritis.

La respuesta a los tratamientos en la readmisión fué en total satisfactoria, pero lenta.

La causa mas común sospechada de la recaída, fué tratamiento insuficiente en pacientes predispuestos a la recaída, porque estaban sufriendo de lepra límite (borderline), o de lepra mostrando aspectos atípicos.

#### RÉSUMÉ

Durant la période s'étendant de 1958 à 1964, 51 malades qui avaient reçu l'exeat après avoir été reconnus indemnes de symptômes (ce qui représente environ 6%) ont été réadmis, à la suite de rechutes, à la léproserie d'Uzuakoli pour y être traités.

La classification initiale de ces malades avait été: 14 lépromateuse, 22 borderline, 6 tuberculoïdes, 9 indéterminés. Toutefois, si l'on s'en tient à la description clinique, les lésions de 4 malades atteints de lèpre lépromateuse, de 2 avec lèpre tuberculoïde, et de 9 souffrant de la forme indéterminée de l'affection, témoignaient de caractéristiques atypiques qui les rattachaient au groupe borderline. Les examens bactériologiques et histologiques corroboraient étroitement les observations cliniques.

Aucun traitement, ou combinaison de traitements, n'a paru plus particulièrement apte à être suivi de rechute. La durée du traitement avait été courte si l'on se réfère aux conceptions modernes.

La rechute est survenue endéans une période d'un an après l'exeat chez 14 malades, endéans 2 ans chez 8 autres.

Quatorze malades seulement avaient fait preuve de régularité en ce qui regarde l'examen périodique après exeat.

Outre les manifestations cutanées de récidence (apparition de nouvelles lésions et réactivation des lésions anciennes), la caractéristique la plus sérieuse de la récidence a été la prédominance d'une polynévrite grave et étendue.

La réponse au traitement après réadmission a été dans l'ensemble satisfaisante, quoique lente.

La cause la plus courante de la récidence est, à ce que l'on soupçonne, un traitement insuffisant chez un malade prédisposé aux rechutes du fait qu'il est atteint de lèpre borderline, ou de lèpre présentant des caractéristiques non typiques.

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