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Bacterial Negativity and Reactivation (Relapse) of Lepromatous Outpatients Under Sulfone Treatment[1]

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From the epidemiologic and administrative points of view there is great interest in determining the time required to obtain bacterial negativity of lepromatous patients and the duration of treatment before releasing them from control ("Rayé de contrôle," "alta definitiva"). The Committee on Therapy of the VII International Congress of Leprology, Tokyo (7) emphasized the need to study the frequency of relapses, before definite rules can be laid down regarding the length of time for which maintenance therapy should be continued.

In line with the above recommendation, this study had two main objectives:

1. To determine the time required to obtain bacterial negativity (inactivity[3]) of lepromatous patients treated with sulfones.
2. To find out the cumulative coefficient of bacterial reactivation[4] (relapse[5]) of lepromatous patients after achievement of inactivity and while still under sulfone treatment.

Additional objectives included the following:

1. To determine the period of time required for achieving bacterial negativity of reactivated patients.
2. To ascertain whether there is correlation: (a) between the time required for the achievement of bacterial negativity and that for bacterial reactivation, (b) between the time required for the reactivation and that for subsequent bacterial negativity.
3. To find out the cumulative coefficient of cases reactivated twice.

It should be stressed that the data were obtained in a dispensary under routine, everyday conditions and as such may give an idea of what may be achieved in outpatient care of lepromatous cases in centers of the same standard. The same observer (R.Q.) followed the cases for a period of about 20 years. Therefore, this is a retrospective study and the data derive from the natural development of a routine project and not from a specially designed investigation.

Faget (5), Souza Lima *et al.* (14) and others have indicated the time required to obtain bacterial negativity in lepromatous patients treated in sanatoria, where the administration of sulfones and follow-up may be carried out in ideal conditions. There are few similar studies in relation to outpatients (10) though this is most important, since the control of leprosy has shifted from inpatient to outpatient care and it is necessary to know how long it may take to decrease the load of infectiousness in leprosy control projects of different standards. The better the standard the nearer the results will be to those obtained in sanatoria, indicating that a high proportion of patients are regularly treated.

The second main objective of our study—determination of the proportion of bacterial reactivation of inactive ("arrested") lepromatous cases despite continuing treatment—

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3 A leprosy patient without any sign of clinical activity and with negative bacteriologic examinations should be considered as an "inactive case"(16).

4 The cumulative coefficient of bacterial negativity is explained in Table 1 where the life-table technic has been used to compute probabilities of a patient showing bacterial negativity during successive time-intervals. In this sense R_x denotes the probability that a patient who is initially bacteriologically positive will be bacteriologically negative at the end of a time-interval x. The cumulative coefficient of reactivity is based on a similar concept.

5 The Committee on Treatment of the VIth International Congress of Leprology (6) used both "reactivation" and "relapse" in the same sense.

is also of the utmost importance, especially from epidemiologic and administrative points of view. The duration of treatment of leprosy cases of different forms is, or must be, determined in leprosy control projects and the main difficulty concerns lepromatous patients. For this reason, the Committee on Therapy of the Tokyo Congress ([7]) recommended investigation of this subject: "Whichever method of treatment is used, it is important that therapy should continue for some time after clinical and bacteriologic resolution of the disease, but more data regarding the frequency of relapses are required before definitive rules can be laid down regarding the length of time during which maintenance therapy should be continued." This recommendation was motivated by the fact that only a few papers had been published on this subject, ([4, 8, 11, 12, 13]). This is understandable because these are long-term studies which should last for some 20 years, with the same standard of accuracy in relation to clinical and bacterial examinations and if possible with the same investigator. Other difficulties are those of case-holding of patients for 10-20 years, and the assurance of regularity of treatment of outpatients which constitutes the major problem in outpatient care.

In this retrospective study an attempt is therefore made to provide data on the objectives of this paper, with all the reservations related to the relevant difficulties.

MATERIALS AND METHODS

A previous paper ([12]) dealt chiefly with lepromatous patients discharged from sanatoria after they became inactive ("arrested," "blanchis," "branqueados") and grouped (in cohorts) according to the year of registration in the dispensary. A small number of patients transferred from sanatoria to the dispensary while bacteriologically positive and some early or moderately advanced lepromatous cases were also followed until they became inactive.

In the present study all the lepromatous cases registered in the dispensary were considered. The study encompasses 815 patients in two categories: (1) patients who began treatment in 1946 in sanatoria from which they were later discharged to dispensary care; (2) those who have received outpatient care since their registration.

Disease groupings. The disease status when treatment was begun varied from patient to patient, and this may explain the different behavior of cohorts previously noted ([12]). Therefore, it seemed advisable to group the cases according to the severity of the disease at the beginning of treatment. There is no agreement among leprologists on this matter, as reflected by the fact that the Committees on Classification in International Congresses have not been able to propose a sub-classification of lepromatous cases that could be accepted and /or approved by the participants. In our attempt the following personal criteria were adopted.

Early lepromatous patients (L1): Present erythema and infiltration without lepromas; nasal smears usually negative and skin smears bacteriologically positive.

Moderately advanced lepromatous patients (L2): Erythema and infiltration in extensive areas of the body, sparse lepromas. Skin smears positive and nasal smears usually presenting bacilli.

Advanced lepromatous patients (L3): Generalized erythema, infiltration and numerous lepromas. Nasal and skin smears strongly positive.

Diagnosis and classification were made on clinical and bacteriologic grounds. The majority of patients had histopathologic examination and had been lepromin tested. Patients, bacteriologically negative for two or more years and treated for five or more years, had a new histopathologic examination.

Treatment schedule. Sulfone treatment was given in accordance with the schedules in use in the leprosy dispensaries of the State of São Paulo.

1. ***Oral route***: (a) Diaminoxyl Butantan (a product similar to Diamidin and Diasone): 2-3 tablets per day (0.33 gm. of disubstituted sulfone in each tablet). (b) A.M. (Butantan, parent sulfone DDS 100 mgm. in each tablet) 1-2 tablets per day.

Taken for 20 days with 10 days rest or continuously.

2. ***Parenteral route***: (a) Intravenous—sulfenona (Butantan, similar to Promanid P.D.): maximum of 12.5 ml. per day excep-

TABLE 1. *Lepromatous leprosy L1 = "regular" treatment time for achieving bacterial negativity.*

X	Lx	Rx	Px	Qx	Sx	Rx 1	Tx
0.0–0.5	193	25	0.8704	0.1295	0.8704	0.1295	9
0.5–1.0	159	39	0.7547	0.2452	0.6569	0.3430	6
1.0–1.5	114	30	0.7368	0.2631	0.4840	0.5159	3
1.5–2.0	81	17	0.7901	0.2098	0.3824	0.6175	4
2.0–2.5	60	15	0.7500	0.2500	0.2868	0.7131	2
2.5–3.0	43	11	0.7441	0.2558	0.2134	0.7865	0
3.0–3.5	32	10	0.6875	0.3125	0.1467	0.8532	0
3.5–4.0	22	6	0.7272	0.2727	0.1067	0.8932	1
4.0–4.5	15	2	0.8666	0.1333	0.0925	0.9074	0
4.5–5.0	13	1	0.9230	0.0769	0.0853	0.9146	0
5.0–5.5	12	0	1.0000	0.0000	0.0853	0.9146	0
5.5–6.0	12	4	0.6666	0.3333	0.0569	0.9430	0
6.0–6.5	8	1	0.8750	0.1250	0.0498	0.9501	0
6.5–7.0	7	1	0.8571	0.1428	0.0426	0.9573	0
7.0–7.5	6	0	1.0000	0.0000	0.0426	0.9573	0
7.5–8.0	6	0	1.0000	0.0000	0.0426	0.9573	0
8.0–8.5	6	0	1.0000	0.0000	0.0426	0.9573	0
8.5–9.0	6	1	0.8333	0.1666	0.0355	0.9644	0
9.0–9.5	5	0	1.0000	0.0000	0.0355	0.9644	0
9.5 and over	5	1	0.8000	0.2000	0.0284	0.9715	4

ting Saturdays and Sundays, (b) Intramuscular—A.M. (Butantan, parent sulfone, 10% suspension): 2 injections of 1 or 2 ml. per week.

Up to a few years ago the drug was administered for 20 days followed by 10 days of rest, but later treatment was uninterrupted. Full treatment was never stopped after inactivity had been achieved. Oral DDS was the most common treatment.

"Regular" and "irregular" treatment. Outpatient clinic patients were periodically examined, monthly or quarterly, or also half-yearly when they had been inactive for more than two years and this status had been confirmed by a histopathologic examination. Thereafter, since continuing drug treatment took place at home, it was not possible to know whether two-thirds or more of the total doses prescribed was taken or the regularity of intake. Confronted with this difficulty, patients were divided into two groups:

(1) in which patients attended the periodical follow-up examinations regularly and where home visitation verified perscribed treatment regimen;

(2) patients who did not attend follow-up regularly and whose irregularity in treatment was evident. A patient was considered irregular in treatment when: (a) he did not attend the follow-up examination regularly; (b) drug intake ceased, or (c) domiciliary visits noted that the drug had not been taken according to prescription.

It should be stressed that under Brazilian law treatment is compulsory. Legal measures are not taken but patients are obliged to undergo biannual examinations in order to obtain a certificate entitling them to receive state or federal benefits. When irregular they were visited.

Probationary period. Previously [12] bacterial negativity was regarded as established if confirmed in the following six months. In the present study this period was extended to 12 months. After this if the patient became bacteriologically positive, his disease was considered reactivated.

Patients were released from control by a Federal Committee after five years of inactivity. However, they also had to have a 2+ or 3+ Mitsuda reaction (induration or nodule more than 5 mm. or ulceration) before being released. Lepromatous cases, therefore, are treated for life.

Follow-up examinations. As indicated previously, patients were periodically examined (skin and nerves) monthly, quarterly or half-yearly. At such times a doctor (R.

Q. or one of his colleagues), or technician under medical supervision, systematically collected material from nasal mucosa and from lesions suspected to be active; in inactive cases material was collected from areas previously positive (ear lobes, elbows).

Bacterial examination. During 20 years, only four technicians in groups of two, one senior and one junior, have examined the slides. Smears were stained by the Ziehl-Neelsen method. A smear was considered negative after 80 fields had been examined. Grading was done in accordance with the recommendations of II Pan-American Conference of Leprosy ([9]).

The morphologic index, introduced recently, was not utilized.

Statistical methods. The modified life-table method was used, grouping the patients according to degree of progression of the disease (L1, L2 and L3), regular attendance at follow-up examinations and irregularity of treatment (6 groups). Previously ([12]) age and sex had not influenced the results, consequently in this study these were not taken into account and a greater number of cases is available in each of the six groups.

The data were analyzed with the use of a computer and modified life-tables calculated according to the years of treatment (Table 1).

Statistical analysis. The comparison of probabilities of nonbacterial negativity up to X years of treatment and according to regularity or irregularity of treatment was made in accordance with the formula ([2]):

$$Z = \frac{S_{x,\,R} - S_{x,\,I}}{V(S_{x,\,R}) + V(S_{x,\,I})}$$

The factor Z has an approximately standardized normal distribution where:

$S_{x,\,R}$ = probability of nonnegativity up to x years of "regular" (?) treatment.

$S_{x,\,I}$ = probability of nonnegativity up to x years of irregular treatment.

$$V(S_{x,\,R}) = S^2_{x,\,R}\,x - 1 \sum_{n\,=\,0} \frac{qn^2}{Pn.Rn}$$

= variance of $S_{x,\,R}$

Only the data of the modified table for lepromatous cases L1 under "regular" treatment and time required for bacterial negativity are given as an example (Table 1) The key to the symbols is as follows:

x = time (years);

Lx = number of patients under observation at the beginning of interval time x;

Rx = number of cases with bacterial negativity during the interval x;

Px = probability (expressed in percentage) of a patient not showing bacterial negativity during the interval x;

TABLE 2. *Cumulative coefficients of bacterial negativity in patients attending follow-up examinations regularly and in those irregularly treated. (Irrespective of possible subsequent reactivation.)*

Grade of severity	"Regular" treatment							Irregular treatment						
	No. cases	Cumulative coefficients at the end of						No. cases	Cumulative coefficients at the end of					
		1 yr	2 yr	3 yr	5 yr	9.5 yr	over 9.5		1 yr	2 yr	3 yr	5 yr	9.5 yr	over 9.5
L1	193	34	62	79	91	96	97	30	20	43	60	69	84	—
L2	286	4	23	46	74	94	99	49	0	12	22	53	80	92
L3	211	0	2	11	44	83	97	46	0	0	4	15	59	74

Qx = probability (expressed in percentage) of a patient presenting bacterial negativity during the x interval; this value is the complement of Px;

Sx = cumulative coefficient of non-bacterial negativity until the end of the interval x; this value is calculated by multiplying the value of Px by those corresponding to the previous intervals;

Rx 1 = cumulative coefficient of bacterial negativity until the end of the interval x; this value is the complement of Sx;

Tx = number of patients withdrawing from follow-up at the end of the interval x (death, transference to another dispensary or to a leprosy sanatorium).

RESULTS

Time required for obtaining bacterial negativity in lepromatous patients (Table 2 and Fig. 1). Of 815 patients, 690 regularly came for follow-up examinations while 125 were irregularly treated. The results have a certain pattern indicating that under "regular" treatment and in early lepromatous cases (L1) the cumulative coefficient of bacterial negativity is higher than in irregularly treated cases and in more advanced patients (L2 and L3). Statistical analysis showed that the probability of occurrence of bacterial negativity was always higher in the groups of patients attending follow-up examinations regularly.

Among patients treated "regularly" at the end of two years—the cumulative coefficient of bacterial negativity was 62 for L1 patients and only 23 for L2 and 2 for L3. Among patients treated irregularly the cumulative coefficient was respectively 43, 12 and 0.

These comparisons were made at significance level of 5 per cent for lepromatous leprosy L1, L2 and L3 until 1, 2 and 3 years respectively, with the following results for Z:

Lepromatous leprosy	X years	Z
L1	1	2.75
L2	2	2.07
L3	3	2.15

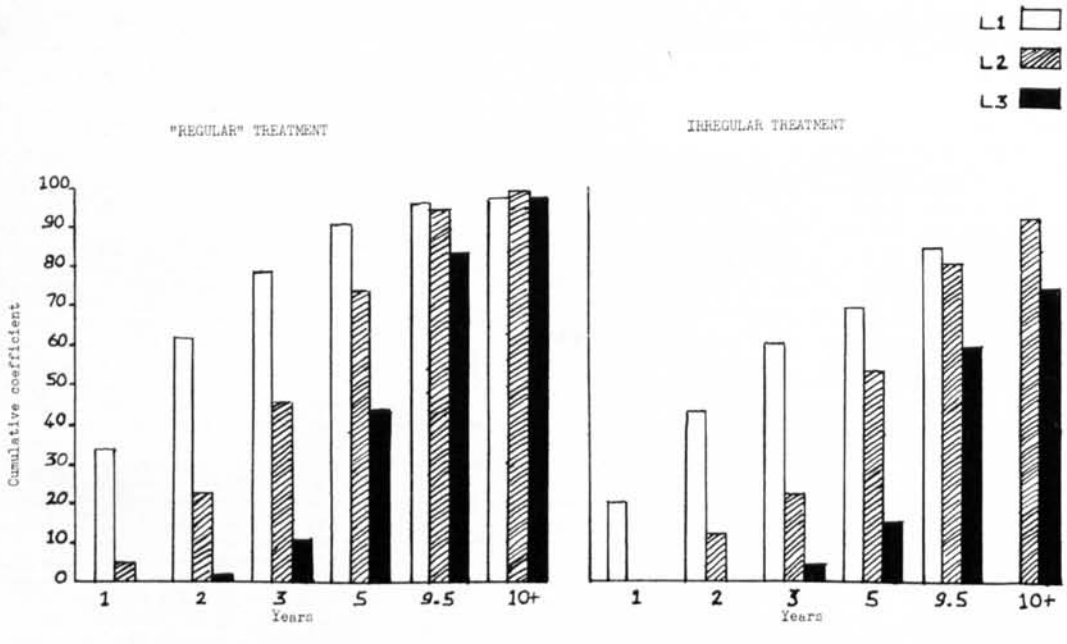

FIG. 1. Bacterial negativity of 815 lepromatous patients under sulfone treatment (1946-1967). Dispensary of Campinas, São Paulo, Brazil.

TABLE 3. *Cumulative coefficients of reactivation of lepromatous patients attending follow-up examinations regularly and in those irregularly treated.*

Grade of severity	"Regular" treatment							Irregular treatment						
	No. cases	Cumulative coefficients at end of						No. cases	Cumulative coefficients at end of					
		1 yr	2 yr	3 yr	5 yr	9.5 yr	over 9.5		1 yr	2 yr	3 yr	5 yr	9.5 yr	over 9.5
L1	163	1	1	4	8	19	27	22	0	0	5	11	34	56
L2	235	0	2	4	12	27	29	39	0	0	6	29	56	88
L3	183	1	3	6	14	27	37	32	0	3	7	28	62	86

All these values were significant when compared with the critical value of 1.64.

Therefore, as expected the "regularity" of treatment was superior in the three comparisons, i.e., the probability of bacterial negativity was already higher in the group "regularly" treated.

Since the probabilities of nonnegativity decrease as the period of treatment increases either in those treated "regularly" or in those treated irregularly (this is true for L1, L2 and L3) we should have begun the comparison of probabilities starting with the first year. If for this determined X the difference had been significant, i.e., the "regular" treatment superior to the irregular one regarding the chance of negativity, then the differences found for the values greater than X, i.e., 2, 3 . . . years of treatment, would be significant. Therefore, in this case, we should not need to undertake the comparisons, i. e., the tests of hypothesis for the values of $X > 1$ year.

In the opposite case, i.e., if the differences between the probabilities of nonnegativity had not been significant for $X = 1$ year, we should continue with the comparisons until we find that value of X for which a difference would be significant.

Taking this into account, we started with $X = 1$ for lepromatous L1 and since the difference found was significant we stopped there; for lepromatous leprosy L2 we could not start with $X = 1$ because in correspondence to irregular treatment Q_x was 0.0000 giving null variance for $S_{X,L}$. For this reason we started from $X = 2$ and for the same reason began with $X = 3$ for the comparisons of treatment regarding lepromatous leprosy L3.

Over nine and a half years of "regular" treatment were required for L2 and L3 cases to reach a similar proportion of negativity as in L1 patients at the end of five years. Since the figures refer to cumulative coefficients, they do not indicate, at a certain date (e.g., at over 9.5 years) that practically all patients were negative on that occasion. In fact it should be pointed out that many of the cases rendered inactive had a reactivation in the period of observation and again obtained bacterial negativity under treatment.

Cumulative coefficient of bacterial reactivation of inactive ("arrested") lepromatous cases still receiving sulfone treatment (Table 3 and Fig. 2). Since the regulations for releasing a patient from control ("rayé de contrôle," "alta definitiva") require at least a 2+ Mitsuda reaction, most lepromatous cases are kept under control and treatment, because this requirement is seldom met by these patients in Brazil.

The cumulative coefficients of reactivation at the end of the observation periods do not signify that the same proportion of patients is still positive. Following intensification of treatment, inactivity may again be achieved. The results show a pattern which is not as evident as that relating to bacteri-

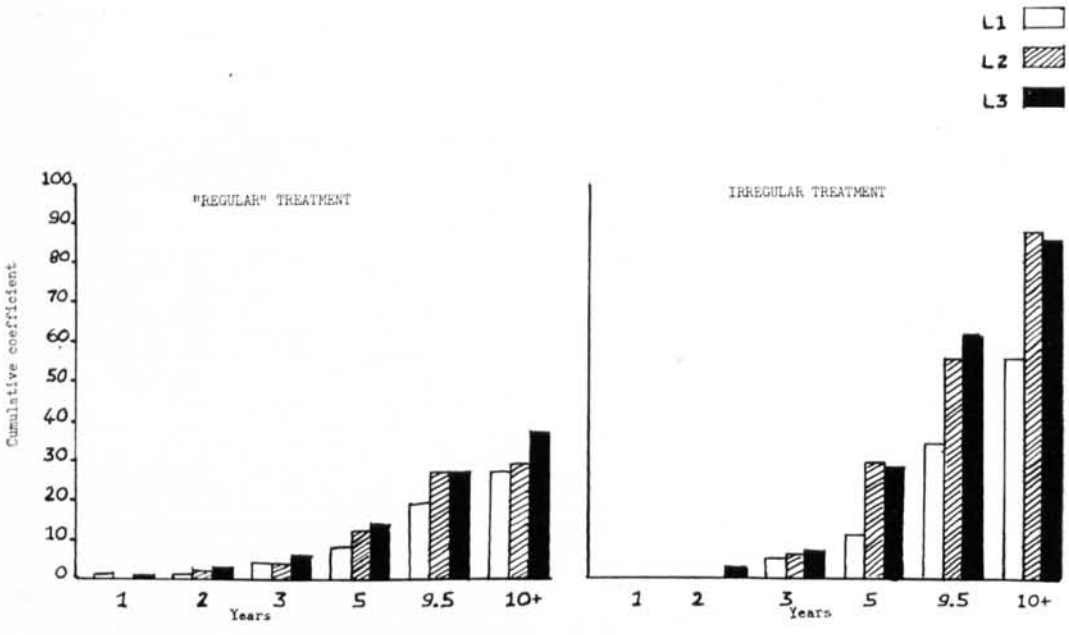

FIG. 2. Bacterial reactivation of 815 lepromatous patients under sulfone treatment (1946-1967). Dispensary of Campinas, São Paulo, Brazil.

al negativity (Table 2). It indicates that the cumulative coefficients of reactivation, though relatively low after three or five years, were high after nine, ten or more years and much higher among patients treated irregularly (56, 88 and 86 respectively for L1, L2 and L3 after 9.5 or more years of irregular treatment). It is also noted that the coefficients of reactivation in respect to groups of patients irregularly treated. When considering only the group of patients "regularly" treated, the coefficients were not strikingly different in L1, L2 and L3 though the results seem more favorable for L1. This suggests that if adequate treatment is continued after inactivity is achieved, it appears to be similarly effective in lepromatous patients in preventing reactivation regardless of their degree of severity when therapy was begun.

TABLE 4. *Results of histopathologic examinations in inactive lepromatous cases with bacterial negativity for at least two years and treated for at least five years.*

Histopathologic structure	Skin acid-fast bacilli		Total
	Negative	Positive	
Lepromatous, in regression	12	24	36
Chronic inflammatory infiltrate	159	11	170
Total	171	35	206

The cumulative coefficient of reactivation is much higher after five or more years of inactivity as compared to that of the first five years of follow-up; this is most evident among the irregularly treated patients. Therefore, papers dealing only with five years of follow-up after inactivity would not be able to give the real picture of the frequency of relapses.

Histologic examination of skin lesions from inactive lepromatous cases with bacterial negativity for at least two years and treated for at least five years. Inactive lepromatous cases fulfilling these conditions had skin biopsies to obtain the "alta provisoria" which entitled them to some advantages, including half-yearly follow-up examinations.

The results of histopathologic examinations of biopsy specimens from 206 patients still continuing in the dispensary are noted in Table 4.

Among 206 cases, 35 still were bacteriologically positive and 36 had lepromatous structure in regression. In the latter the proportion of positivity was much higher than in the patients with chronic inflammatory infiltrate in skin sections. Twenty of the 159 patients with chronic inflammatory infiltrate and negative bacteriologic findings in skin sections later became bacteriologically positive despite continuing sulfone therapy.

These data and the known finding of bacilli in viscera (autopsy and needle biopsy), lymph nodes, bones and in the musculi erectoris pilorum of inactive lepromatous cases together with knowledge of the limited action of sulfones and other drugs explain the high proportion of reactivation, especially when treatment is irregular.

Bacterial reactivation occurs because a substantial proportion of inactive cases are not completely freed of leprosy bacilli. More refined methods (e.g., concentration technics) can show then in the skin. Cottenot *et al.* ([3]) used a simple technic of concentration which in 20 patients was compared with the classic method of staining skin smears. They reported that both were negative in 10 cases; of the remaining 10 patients, three showed bacilli by both methods and seven only after concentration.

TABLE 5. *Time required for the achievement of bacterial negativity and that for subsequent reactivation. (Values of the coefficients of correlation of "T" test in relation to L1, L2 and L3 and treatment.)*

Grade of severity	Treatment	r	t
L1	"regular"	0.12	0.52
	irregular	−0.40	−0.98
L2	"regular"	−0.16	−1.02
	irregular	−0.02	−0.08
L3	"regular"	−0.09	−0.63
	irregular	−0.34	−1.59

Is there a correlation between the time required for the achievement of bacterial negativity and for subsequent bacterial reactivation? Theoretically it might be assumed that given the same disease progression and the same dose of sulfones and regularity of treatment, patients who obtain bacterial negativity more quickly have responded better to treatment and have better mechanisms of defense than the others. Therefore they would be less likely to reac-

TABLE 6. *Bacterial negativity of reactivated patients.*

Type	Treatment	No. reactivated cases	Cumulative coefficient of negativity at the end of				
			1 yr	2 yr	3 yr	4 yr	5 yr
L1	"regular"	15	53	62	72	81	81
	irregular	5	40	40	40	100	100
L2	"regular"	38	50	61	67	81	100
	irregular	25	25	41	47	53	59
L3	"regular"	43	35	40	49	62	68
	irregular	21	9	15	15	33	42
		147					

tivate and this reactivation would occur late if treatment is continued regularly.

A study of this problem is difficult primarily because of the variations in dosage, rhythm and regularity of treatment, as well as individual absorption of the sulfone. With these reservations in mind, 144 reactivated cases were studied. the values of the coefficient of correlation of the size of samples and of the Student "t" test, according to groups L1, L2 and L3 and regularity of treatment are shown in Table 5 and they were not significant. Consequently in the material studied there was no correlation between the time required for inactivity and that for the subsequent reactivation.

Period of time required for achieving bacterial negativity in reactivated patients (Table 6). Data from 147 reactivated patients were studied by the modified lifetime method. The results are given in Table 6. These are presented with reservation because the number of patients of each group (L1, L2 and L3) treated regularly or irregularly is small. At the end of the first year of the reactivation, about 50 per cent of the patients under "regular" treatment were bacteriologically negative in the L1 and L2 groups, and 35 per cent negative in the L3 cases. In the patients treated irregularly these proportions were respectively 40 per cent, 25 per cent and 9 per cent. The reactivated cases were strongly warned about the dangers of neglecting treatment, and the results appear to have been influenced by the degree of treatment regularity and the dosages of DDS employed.

It was previously reported ([12]) with different methodology, that reactivated patients achieved negativity more rapidly (83% and 94% at the end of the first and second years respectively) than now noted. However, as previously indicated, the probationary period was only six months long.

TABLE 7. *Time required for reactivation and subsequent negativity values of the coefficients of correlation of "T" test in relation to L1, L2 and L3 and treatment.*

Lepromatous leprosy	Treatment	r	t
L1	"regular"	0.14	0.52
	irregular	—	—
L2	"regular"	0.08	0.47
	irregular	0.01	0.05
L3	"regular"	−0.23	−1.12
	irregular	−0.77	−2.74

TABLE 8. *Second reactivation. Time elapsed since the achievement of second period of inactivity.*

Lepromatous	Treatment	No. inactive cases	Cumulative coefficient of second reactivation at the end of					
			1 yr	2 yr	3 yr	5 yr	over 9.5	No. of 2nd reactivation
L1	"regular"	12	0	9	9	20	20	2
	irregular	2	—	—	—	—	—	0
L2	"regular"	31	0	0	8	13	37	5
	irregular	13	0	9	19	19	63	5
L3	"regular"	26	0	5	5	17	29	2
	irregular	7	14	14	31	82	82	5
		91						19

From our data it is evident that the period of time required for achieving the second inactivity is much shorter than that for the first inactivity regardless of disease severity.

Is there a correlation between the time required for reactivation and that for achieving subsequent bacterial negativity? Theoretically it may be assumed that with the same degree of progression of the disease and the same schedule and regularity of treatment, the longer the time elapsing before reactivation the shorter might be the time required for achieving bacterial negativity.

Comments in the above section on bacterial reactivation are also valid here. The data in Table 7, concerning only 80 cases, are presented with great reservation. The analysis of this distribution was also made by the Student "t" test. The values of the coefficients of correlation of sample L1, L2 and L3 and of "t" test are shown in Table 7. As in Table 5 there is no significant correlation between these two factors.

Cumulative coefficient of cases reactivated twice. The 91 reactivated patients who subsequently achieved a second period of inactivity have been followed. Nineteen of them again became bacteriologically positive. The data studied by the modified life-table method are assembled in Table 8 but should be considered with great reservation because the number of cases is small.

It seems that the frequency of second reactivation tends to be higher among patients irregularly treated and among L3 cases. It also appears that the frequency of second reactivation is high, mainly in the 5-year or "over 9.5 years" groups after the second inactivity had been achieved and despite apparently continuing treatment.

Both first and second reactivations are most probably due to the fact that patients, even those supposed to be "regularly" treated, slow down treatment when they become inactive ("arrested"). These results also confirm the limited efficacy of sulfone treatment with regard to lepromatous cases.

DISCUSSION

The data presented—especially concerning the two main items of this paper—are very important from the epidemiologic and administrative points of view. They confirm the great length of time required for achieving bacterial negativity, especially in the most advanced lepromatous cases. Almost all L1 cases achieve bacterial negativity by the end of five years. Similar results are observed in L3 only after 9.5 years or more. The difficulties in keeping patients under regular treatment for such long periods are apparent and have been noted by Bechelli [1]. This is aggravated by the occurrence of bacterial reactivation despite treatment, after five years or even after 10 or more years, even if inactivity may again be achieved in a relatively short period.

The persistence of "open cases for so many years explains the maintenance of endemics for decades. In the Campinas region, in which the control activities have been satisfactorily developed since 1928,

TABLE 9. *Detection rate of leprosy cases in Campinas and other municipalities of the same region, 1950–1965.*

Area	Period	Population	No. cases	Rate/ 1,000	% leprosy cases
Campinas	1950–55	136,723	150	1.1	64
	1955–60	219,303	153	0.69	63
	1960–65	249,674	177	0.70	61
Other municipalities of same region	1950–55	54,692	31	0.54	69
	1955–60	94,386	47	0.49	44
	1960–65	101,037	89	0.90	53

and in spite of the remarkable socio-economic progress, the yearly detection rate and the proportion of lepromatous cases continues to be high (Table 9).

The relative inefficiency of sulfone therapy is a major factor. Additionally the control of leprosy may be delayed for decades by low standards of living and education at all levels of the population. A way to overcome these difficulties rapidly would be the discovery of a new and more effective drug and/or of an immunizing agent.

The frequency of reactivation in the first five year period of inactivity is relatively small as compared to the cumulative coefficient in the subsequent period (over 5 years). Therefore, in studies designed to investigate reactivation or relapse, the follow-up of inactive lepromatous cases should not stop at five years but should be extended to at least 10 years.

Another aspect to be considered in relation to the reported data is the duration of treatment for inactive ("arrested") cases before they are released from control ("rayé de controle", "alta definitiva").

The Committee on Treatment of the Madrid Congress ([6]) made the following statement concerning the management of "arrested" cases: "Recent observations suggest that arrested cases are not completely freed of leprosy bacilli, and that reactivation of the disease is therefore not unlikely. Continuing observation is indicated in all 'arrested' cases in order that any reactivation may be detected as soon as possible.

"Continuing treatment of 'arrested' cases may reduce the relapse rate and with oral administration of the drug, continuing treatment can be very simple. It is recommended in those areas where it is practicable".

In Brazil, and also in Venezuela, lepromatous cases must present at least a 2+ Mitsuda reaction before they are released from control. This means that treatment and follow-up should continue for life for the great majority of them.

For administrative purposes, taking into account the data of Rodriguez ([13]) and Quagliato *et al.* ([12]) the WHO First Regional Seminar on Leprosy Control ([17]) tentatively recommended that once inactivity of lepromatous cases is achieved, full treatment should be continued for five years before the patient is released from control. In the same year, this was endorsed by the WHO Expert Committee on Leprosy ([16]).

The data now presented fully support the Brazilian and Venezuelan regulations concerning the release from control of lepromatous cases. Perhaps the results are also applicable to other South American countries or wherever leprosy has the same characteristics.

If the data now reported are confirmed in other areas of the world the periods for releasing lepromatous cases from control should be extended to at least 10 years after inactivity (for life?). Considering that lepromatous cases constitute the principal source of infection and that their treatment and follow-up deserve first priority in leprosy control, provision should be made for their regular treatment and surveillance for very long periods after inactivity is achieved.

SUMMARY AND CONCLUSIONS

Data are presented regarding the treatment and follow-up of 815 lepromatous outpatients from 1946 to 1968. They were mainly treated with oral DDS 100-200 mgm. though Diaminoxil (2-3 tablets daily) or DDS by parenteral route was also used. Lepromatous cases were classified according to the degree of progression of the disease into three groups and the results of treatment related thereto. The data were analyzed with the use of a computer and modified life-tables calculated according to the years of treatment.

With the reservations related to the relevant difficulties in long-term retrospective study, the conclusions were as follows.

The probability of occurrence of bacterial negativity was always higher for patients who regularly attended the follow-up examinations ("regular treatment").

There is a certain pattern indicating that under "regular" treatment and in early lepromatous cases (L1) the cumulative coefficients of bacterial negativity are higher than in irregularly treated cases and in more advanced lepromatous patients (L2 and L3). At the end of two years the cumulative coefficient of bacterial negativi-

ty was 62 for L1 patients treated "regularly" and only 23 for L2 and L3 treated "regularly." Among patients treated irregularly, these coefficients were respectively 43, 12 and 0.

The cumulative coefficients of reactivation (relapse) were very high after nine or more years and much higher among patients treated irregularly (56, 88 and 86 respectively for L1, L2 and L3 after 10 or more years of irregular treatment). The cumulative coefficient or reactivation was higher after five or more years of inactivity when compared with that of the first five years of follow-up.

Among 206 inactive ("arrested") cases during two or more years and treated for at least five years, 35 still were bacteriologically positive and 36 had lepromatous structure in regression in skin sections. Twenty of 159 patients with chronic inflammatory infiltrate and negative bacteriologic examination by skin sections had later bacterial reactivation despite apparently continuing sulfone therapy.

Of 147 reactivated patients after one year of "regular" treatment, the proportion of bacterial negativity was 53 per cent, 50 per cent and 35 per cent respectively in L1, L2 and L3 cases. In the patients irregularly treated these proportions were 40 per cent, 25 per cent and 9 per cent. The period of time required to achieve the second disease arrest was much shorter than that for the first.

There was no correlation between the time required for inactivity and that for subsequent reactivation.

There was no correlation between the time required for reactivation and that for achieving subsequent bacterial negativity.

It appears that the frequency of second reactivation (relapse) is higher, even after five or 10 years after a second period of disease arrest has been achieved and in spite of apparently continuing treatment. The frequency tends to be higher among patients treated irregularly and among L3 cases.

The epidemiologic and administrative implications of the data reported are discussed in relation to leprosy control. It is concluded that if these findings are confirmed, lepromatous patients who achieve bacterial negativity (inactive, "arrested" cases) should continue regular treatment for at least 10 years before being released from control. The results reported give support to the leprologists who think that, with present antileprosy drugs, lepromatous cases should be treated for life.

RESUMEN Y CONCLUSIONES

Se presentan datos en relación con el tratamiento y control posterior de 815 pacientes lepromatosos en tratamiento ambulatorio, desde 1946 hasta 1968. En su mayor parte fueron tratados con DDS oral, 100–200 mgm. aunque también se usó Diaminoxil (2-3 tabletas diarias) o DDS por vía parenteral. Los casos lepromatosos se clasificaron, de acuerdo con el grado de severidad de la enfermedad, en tres grupos y los resultados del tratamiento se relacionaron con cada grupo. Los datos se analizaron por medio de una computadora y se calcularon tablas de vida modificadas según los años de tratamiento.

Con las reservas debidas a las dificultades propias de un estudio retrospectivo a largo plazo, las conclusiones son las siguientes.

La probabilidad de encontrar bacteriologías negativas era siempre mayor en los pacientes que acudían en forma regular a los exámenes de control ("tratamiento regular").

Hay un cierto patrón que indica que bajo tratamiento "regular" y en casos lepromatosos iniciales (L1) los coeficientes cumulativos de bacteriologías negativas son más altos que en los casos tratados en forma irregular y en pacientes lepromatosos más avanzados (L2 y L3). Después de dos años, el coeficiente cumulativo de bacteriologías negativas fué de 62 para pacientes L1 tratados en forma "regular" y solamente de 23 para L2 y L3 tratados "regularmente." Entre los pacientes tratados en forma irregular, estos coeficientes fueron respectivamente 43, 12 y 0.

Los coeficientes cumulativos de reactivación (recaídas) fueron muy altos después de nueve o más años y mucho más altos entre los pacientes tratados en forma irregular (56, 88 y 86 respectivamente para L1, L2 y L3 después de 10 o más años de tratamiento irregular). El coeficiente cumulativo de reactivación fué más alto después de cinco o más años de inactividad cuando se comparó con el de los primeros cinco años de control.

Entre los 206 casos inactivos ("arrested") durante dos o más años y tratados por lo menos durante cinco años, 35 todavía eran bacteriológicamente positivos y 36 tenían estructuras lepromatosas en regresión en biopsias de piel. Veinte de los 159 pacientes con infiltrado in-

flamatorio crónico y examen bacteriológico negativo determinado por biopsia de piel tuvieron posteriormente reactivación bacteriana a pesar de que aparentemente continuaban su sulfonoterapia.

De los 147 pacientes reactivados después de un año de tratamiento "regular," la proporción de bacteriologías negativas fué de 53%, 50% y 35% respectivamente en casos L1, L2 y L3. En los pacientes tratados en forma irregular estas proporciones fueron de 40%, 25% y 9%. El período de tiempo que se necesitó para que se produjera el segundo período de inactivación ("arrest") fué mucho más corto que para el primero.

No hubo relación entre el tiempo requerido para que se produjera la inactivación y el tiempo que pasó antes de la reactivación subsiguiente.

No hubo relación entre el tiempo requerido para la reactivación y el necesario para adquirir la negativización bacteriológica subsiguiente.

Es aparente que la frecuencia de segundas reactivaciones (recaídas) es alta, aún después de cinco o diez años que se ha conseguido un segundo período de inactivación de la enfermedad y a pesar de que aparentemente se ha continuado con el tratamiento. La frecuencia tiende a ser más alta entre pacientes tratados irregularmente y entre casos L3.

Las implicaciones epidemiológicas y administrativas de los datos que se presentan se discuten en relación con el control de la lepra. Se concluye que si estos hallazgos se confirman, los pacientes lepromatosos que presentan bacteriología negativa (casos inactivos "arrested") deben continuar con tratamiento regular durante por lo menos 10 años antes de ser liberados de control. Los resultados encontrados sirven de apoyo a los leprólogos que piensan que, con las drogas antileprosas de que se dispone por el momento, los casos lepromatosos deben tratarse durante toda la vida.

RÉSUMÉ

On présente ici des données qui se rapportent au traitement et à la surveillance continue de 815 malades lépromateux ambulatoires, de 1946 à 1968. Ces malades ont été principalement traités par la DDS administrée par voie bucale, à raison de 100 à 200 mg; toutefois du Diaminoxil, à raison de 2 à 3 comprimés par jour, ou de la DDS par voie parentérale, ont également été utilisés. Les cas lépromateux ont été classés en trois groupes, selon le degré d'évolution de la maladie; les résultats du traitement sont rapportés en fonction de cette classification. Les données ont été analysées au moyen d'un ordinateur; des tables de survie modifiées ont été calculées en fonction des années de traitement.

En tenant compte des réserves qu'imposent les difficultés inhérentes à une étude rétrospective de longue durée, les conclusions qui suivent peuvent être tirées. La probabilité d'apparition d'une négativation bactérienne est toujours plus élevée pour les malades qui ont été soumis régulièrement aux examens de surveillance ("traitement régulier").

On a relevé un certain profil qui indique que les coefficients cumulatifs de négativation bactérienne sont plus élevés dans le cas d'un traitement régulier, de même que dans les cas lépromateux précoces (L1), que chez les cas irrégulièrement traités ou chez les malades lépromateux souffrant d'une affection plus avancée (L2 et L3). A la fin de deux années, le coefficient cumulatif de négativation bactérienne était de 62 pour les malades L1 traités régulièrement, et seulement de 23 pour les sujets L2 et L3 également traités de manière régulière. Chez les malades traités de façon irrégulière, ces coefficients étaient respectivement de 43, 12 et 0.

Les coefficients cumulatifs de réactivation (récidive) sont apparus fort élevés après neuf années de traitement ou davantage, et encore plus élevés chez les malades traités régulièrement, (56, 88 et 86 respectivement pour les L1, L2 et L3 après 10 années ou plus de traitement irrégulier). Le coefficient cumulatif de réactivation était plus élevé après cinq années d'inactivité ou davantage, quand on le compare avec celui noté au cours des cinq premières années de surveillance.

Parmi 206 cas inactifs ("arrêtés"), suivis pendant deux années ou plus, et traités pour au moins cinq ans, 35 étaient encore bactériologiquement positifs et 36 présentaient encore une structure lépromateuse en involution dans les coupes de tissu cutané. Parmi 159 malades présentant une infiltration inflammatoire chronique et un examen bactériologiquement négatif sur coupes de tissu cutané, 20 ont présenté plus tard une réactivation bactérienne malgré une thérapeutique sulfonée apparemment continue.

Sur 147 malades réactivés après une année de traitement dit régulier, la proportion de négativation bactérienne s'est élevée à 53 pour cent, 50 pour cent et 35 pour cent respectivement chez les cas L1, L2 et L3. Chez les malades traités irrégulièrement, ces proportions étaient respectivement de 40 pour cent, 25 pour cent et neuf pour cent. L'intervalle de temp nécessaires pour obtenir l'arrêt de l'affection apparue à nouveau, a été beaucoup plus court que pour obtenir l'arrêt de la maladie lors de la première apparition.

On n'a pas noté de corrélation entre le temps requis pour obtenir l'inactivation, et le temps requis pour une réactivation subséquente.

On n'a pas observé davantage de corrélation entre le temps requis pour la réactivation et le temps requis pour obtenir ensuite une négativation bactérienne.

Il est apparu que la fréquence de la deuxième réactivation (recidive) était élevée, même lorsque 5 ou 10 années se sont écoulées depuis l'arrêt de la deuxième période de la maladie, et ceci malgré que le traitement ait apparemment été poursuivi. La fréquence de ces réactivations tend à être plus élevée chez les malades traités irrégulièrement, et parmi les cas souffrant de lèpre L3.

Les implications épidémiologiques et administratives des résultats relatés dans cette étude sont discutées en rapport avec le problème de la lutte contre la lèpre. On en conclut que si ces observations sont confirmées, les malades lépromateux, lorsqu'ils parviennent au stade de négativation bactérienne (cas inactifs ou "arrêtés"), devraient continuer à subir un traitement régulier, pour au moins 10 années, avant d'être déclarés, hors surveillance. Les résultats rapportés fournissent un argument aux léprologues qui pensent que, avec les médicaments antilépreux dont nous disposons à présent, les cas lépromateux devraient être traités pour toute la vie.

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