# RELAPSES AFTER SULFONE THERAPY IN LEPROSY OF THE LEPROMATOUS TYPE<sup>1</sup>

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The need for a proper follow-up of cases rendered clinically and bacteriologically negative by sulfone treatment has been recognized for a long time, but few reports on this subject have appeared so far, due to the great difficulty in gathering data. In leprosy there exist not only the common difficulties inherent to the follow-up treatment of chronic diseases, but there is in addition the unusual prejudice of the public against the disease which compels even those declared free of it to hide.

The aim of this paper is to present a general or birds-eye view of the problem with the purpose of stimulating interest in this matter of the relapses commensurate with its great importance. Consideration of many details have been left out for another paper, including the distinction between clinical, bacteriologic, and combined clinical and bacteriologic relapses. A "relapse" as the term is used in the present paper signifies a positive bacteriologic finding, with or without clinical relapse.

There are two groups of negative patients who had been studied for such relapses, namely: (1) those who have remained in the leprosaria, and (2) those who have been released or discharged from the leprosaria and had been reexamined in their homes by mobile clinics.

The sulfone drugs were introduced in the Philippines after the last World War in 1946, in the form of Promin which the patients themselves had to buy due to the impoverished condition of the country at that time. When limited amounts of money become available, Diasone became the basic drug, although it could be provided for only a limited number of patients. It was not until 1952 that the use of DDS became generalized in the leprosaria. Arrest of the disease among the patients did not reach significant frequency until 1954, and systematic reporting of their follow-up began in 1955.

The rules governing the declaring and control of negatives may be briefly summarized as follows: Lepromatous cases found by their treating physicians to have become clinically and bacteriologically negative are presented to a local "negative committee" which examines the candidates before they are placed on the "negative list." This committee examines all those on the list every three months. After completing a probationary period of six months (later extended to one year), the nega-

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tives become candidates for release, although most of them prefer to remain in the leprosaria until they have completed the full two-years negative period. Those who take advantage of the privilege of release, on the average leave the institutions after a lapse of ten months, the additional period of 4 months being occupied in processing the necessary documents. All those on the negative list have to be examined by a National Disposal Committee at least once (later increased to twice) before release, and twice again (later increased to three examinations) before they can be finally discharged.

Those who are released after the probationary period are required to report for treatment once a week to the nearest leprosy agency, such as a stationary or mobile clinic, or a designated health officer. They are expected to submit also for reexamination every three months. Such continued treatment and observation is required until the completion of the two years negative period.

On the other hand, discharged negatives are required to report to the nearest negative committee for reexamination once every six months for a period of three years, but they are not required to take further treatment although they are advised to do so.

It must be admitted that the large majority of the released and/or discharged negatives fail to follow these directions, and instead try to lose themselves in the general population. As a result, too few of them receive adequate follow-up treatment although it is known that some of them buy their own medicines.

### RELAPSES AMONG NEGATIVES REMAINING IN THE SANITARIA

The findings in the different sanitaria will be briefly presented separately, because conditions vary among them.

The Culion Sanitarium.—There are 2,100 inmates in this institution, formerly named the Culion Leper Colony, of whom about 1,500 are still "open" or bacteriologically positive cases. Just before the last World War, the population was over 5,000 inmates, among whom there were about 250 "burnt-out" patients with negative smears from both the skin and mucous membranes but with typical neural sequelae produced by the damage to the superficial nerve trunks. Many of the latter died from the general deprivation which occurred in the colony during the war, together with large numbers of the other inmates. There have been few admissions to Culion since then, the average being only 50 a year.

The introduction of the sulfones at Culion in 1946 seems to have hastened the production of more "burnt-out" cases among the advanced lepromatous ones, but with much less eye complication, laryngeal involvement, and ulceration of nodules and infiltrations, than in the chaulmoogra period. By the middle of 1955, there were 303 cases approaching the

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"burnt-out" stage, together with other 163 negatives of less than two years period of negativity (Table 1).

The carefully-kept individual records of the treatments at Culion show that the large majority of the inmates, including negatives, receive irregular and insufficient treatment. The main aim of the patients in receiving the treatment appears to be to minimize involvement of the eyes and the larynx and to avoid ulceration of the skin lesions, but not to become negative which would make them liable to be sent back to their homes. Practically all have tried different forms of sulfones, including Diasone or Diamidin, Promin, Sulphetrone and DDS, but only for limited periods of time. There are some, however, who are regular about their treatment. Since 1953 there had been recorded 32 relapsed cases among the negatives at Culion, of which 6 occurred in that year and 1 in 1954, leaving 25 relapses since 1955, as shown in Table 1.

TABLE	1Relapse rate among Culion negatives, according to
	duration of period of observation, 1955 to
	middle of 1958.

Duration of negative period	Av. No. negatives per year	No. of relapses	Relapse rate, 3½ yrs.
Under 6 months	43	3	7.0%
6 months to 2 years	120	16	13.0%
Over 2 years	303	6	1.9%
Relapse rate for negative	es at Culion	4.8%	

The rate of relapse was highest among those who had been negative for 6 months to 2 years, and lowest among those who had been negative over 2 years. This is explained in Table 2 by the fact that most of them are "burnt-out" cases. It will be noted that among an average number of 469 negatives per year reexamined, the relapse rate among them during an observation period of  $3\frac{1}{2}$  years was 4.8 per cent.

Among the average of 303 more or less burnt-out negatives (N2 and N3), there were 5 relapses, or a rate of 1.6 per cent in  $3\frac{1}{2}$  years, while among the average of 166 negatives without marked secondary neural sequelae (N1), there were 20 relapses, or a corresponding rate of 12.1 per cent-almost 8 times as frequent.

In the 32 cases that had relapsed since 1953, only 3 received adequate treatment. Among the rest the treatment was irregular and below the expected minimum dosage. In 2 female negatives, the relapse occurred shortly after delivery.

Central Luzon Sanitarium.—This institution, which is 18 miles north of Manila, has an area of 750 hectares of land. Only about one-half of the inmates live in the dormitories; the others live in their own cottages spread over this large area, close to their gardens. This makes the control of the treatment difficult; there is considerable absenteeism, and there are many escapes. However, the treatment is more adequate than at Culion, and there have been less changes of drugs received by the patients. Most of them had received both DDS and Diasone. The inmate

	Average number of negatives during the year		Number of relapses	
Year	N2 & N3ª	N1 <sup>b</sup>	N2 & N3ª	N1*
1955	300	107	1	2
1956	287	100	3	2
1957	311 .	185	1	11
1958				
1st	313	269	0	5
6 mos.				
Aver- age	303	166	— ·	_
Total relapses		_	5	20

T/	ABLE 2Relapse rates among negatives with preponderance
	of secondary neural manifestations in the lepromatous
	type compared to the rates among those with
	slight or no neural sequelae.

a Approaching the "burnt-out" stage (N2 and N3).

b No marked atrophies or contractures (N1).

population from 1955 to the middle of 1958 averaged 2,100. The cases are also less advanced than those admitted to Culion, and they have included a considerable number of reactional tuberculoid and borderline cases, although the ordinary tuberculoid cases are not admitted. Of all admissions during the period indicated, 96 per cent were voluntary.

There has been a total of 15 relapses from 1955 through the middle of 1958. The rate of relapses, subdivided according to the duration of negative period at time of relapse, is given in Table 3. The average rate of relapse for all groups during the period of  $3\frac{1}{2}$  years was 4.9 per cent.

 
 TABLE 3.-Relapses among the negatives in the Central Luzon Sanitarium.

Duration of negative period	Av. No. negatives per year	No. of relapses	Relapse rate, 3½ yrs.
Under 6 months	67	2	3.0%
6 months to 2 years	136	9	6.6%
Over 2 years	101	4	3.9%

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Eversley Childs Sanitarium.—This institution is very compact, being located within an area of some 22 hectares with little land to spare for gardening. The administration of the treatment therefore is not too difficult to supervise, and the average dose received per patient is probably the highest of all the sanitaria, although it is not perfect due to abuse of pass privileges. The average population during the period of the study was 1,074 inmates. With an average of 174 negatives following sulfone treatment waiting to be released or discharged each year since 1955, only 3 cases are recorded to have relapsed. One was after a negative period of 11 months, another after 1 year and 3 months, and the third after 2 years and 2 months.

Other sanitaria.—There are 3 other sanitaria with physicians in charge whose routine work includes the reexamination of their negatives. The combined population of these sanitaria averaged 1,382 patients per year.

Out of an average of 80 negatives whose duration of negative periods ranged from 3 months to 4 years observed since 1955, only 3 cases are known to have relapsed. One became positive after being on the negative list for 7 months, one for 1 year 6 months, and the third for 1 year 8 months.

## RELAPSES AMONG RELEASED AND DISCHARGED NEGATIVES

The other group of negatives which have been surveyed for relapses were those who had been released and discharged from the leprosaria and were being given treatment by our mobile skin (leprosy) clinics. They were examined consecutively as they were found; in other words there was no selection of the cases studied. Two-thirds (65%) of the 101 cases involved were examined only once, 20 per cent were examined twice, and 15 per cent have been examined three times for the survey. The findings are given in Table 4.

Duration of negative period (months)	Number of negatives	Number of relapses	Per cent of relapses
6 to 11	10	0	0
12 to 23	35	0	0
24 to 35	27	1	3.7
36 to 47	13	1	7.7
48 to 59	2	0	0
60 to 71	2 .	0	0
72 to 83	3	0	0
84 to 95	5	1	20.0
96 to 107	3	0	0
108 to 120	1	0	0
Total	101	3	3

TABLE 4.-Relapses among 101 released and discharged negatives.

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Among the 101 negatives followed-up by the mobile clinics there were 3 relapses. The duration of the negative period of the group ranged from over 6 months to 10 years, but for most of them the elapsed negative period at time of the first reexamination was 1-3 years. One case relapsed among those in the 24-35 months group, one in the 3-4 years group, and one in the 7-8 years group. It was noted that the 3 patients who relapsed were among those who had taken irregular and insufficient treatment (below 70% of the expected treatment attendance). It is also noteworthy that of the 74 cases followed up and treated by the Cebu Mobile Clinic, which had established the best record of treatment attendance of all the mobile units, none had relapsed.

If all the groups are put together, as in Table 5, it will be seen that the number of negatives included in the survey totals 1,125, of which 49 or 4.4 per cent had relapsed at one time or another over variable periods of negativity ranging from 3 months to 10 years. Most of the reexaminations, however, were done between 1 and 3 years of the negative period.

Duration of negative period	Number of negatives	Number of relapses	Per cent of relapses.
Under 6 months	245	5	2.0
6 months to 2 yrs.	385	30	7.8
Over 2 years	495	14	2.8
Total	1,125	49	4.4

TABLE 5.-Relapses among negatives followed up in the Philippines.

Incidentally, in the course of their follow-up of the negatives, the mobile clinics had occasion to reexamine 15 cases derived from the chaulmoogra period whose records show that they have been negative for long periods ranging from 16 to 27 years. Only 2 or 3 were found with slight relapses, but both were found to have become clinically and bacteriologically negative when again examined 7 months later, after receiving DDS treatment.

#### DISCUSSION

The present paper bears the same defects as most of the few previous reports, including insufficient numbers of cases studied, too brief periods of observation, and improper manner of securing relapse rates, all of which are attributable to insufficient data. Based on our recent experience in the follow up of negatives, we believe that it is practically impossible to make an adequate study of relapses unless the job is undertaken as a research project by full-time leprologists and their assistants, provided with sufficient funds, and aided by specialized workers and the regular health personnel in the field who are in a position to render the necessary cooperation.

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It is believed that no government will be able to undertake such research adequately by employing its regular personnel to do this project, in addition to their routine duties and working within the regular budget. This type of undertaking is best done with the help of outside organizations interested in research.

A number of such projects should be undertaken in different parts of the world so that regional variations, if any, may be brought to light and taken into consideration in planning domiciliary or outpatient treatment. It is suggested that the 7th International Congress of Leprology endorse such research projects. In fact, the aim of this paper is to arouse interest which may lead to such an important step. In the last analysis, the success of the sulfone treatment as a tool for the control of the disease depends on this very question of relapses.

There are two important and often-cited reports on the question of relapses following sulfone therapy. The first that was ever published on the subject was that of Erickson who, studying a total of 33 patients with apparent arrest of leprosy who had remained at the Carville leprosarium and had been well followed up for periods varying from 6 months to 5 years, found 5 relapses among 11 negatives who had discontinued the sulfone treatment after becoming negative, but only 1 among 25 patients who had continued treatment, giving relapse rates of 45 and 4.5 per cent, respectively. Those who relapsed formed 18 per cent of the whole group.

The other article is that of Lowe, who reported on the late results of sulfone therapy in Eastern Nigeria. Of the 139 lepromatous cases treated in his Research Unit at Uzuakoli who had been rendered negative, there were 15 relapses, representing 10.8 per cent of the total followed over a span of from a few weeks to 5 years.

In comparing the two results which indicated that relapses were more numerous at Carville than among the Uzuakoli patients, Lowe considered the facts that this group was much larger than that of Erickson, and that the method and period of treatment were not exactly the same. He also felt that the difference might be due also to the fact that the disease tends to be milder among his patients. In other words, the Nigerians show more resistance to the disease than the Americans—which resistance is also indicated, in my opinion, by the greater preponderance of the tuberculoid type over the lepromatous type in Nigeria as compared to other countries. Incidentally, this resistance manifested by certain peoples appears to be associated with severe neural involvement in both the lepromatous as well as the tuberculoid type.

Our incomplete survey indicates at least that the relapses among negatives following sulfone therapy are not as high as those occurring in the past among chaulmoogra-treated negatives. In a personally-conducted study of relapses among chaulmoogra-treated negatives almost 30 years

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ago, the relapse rate was found to be from 30 to 40 per cent (about one-third) among those completing the first 5 years of negative period, while after 10 years, the total reached 75 per cent. Thus, our own experience has been that with intensive chaulmoogra treatment the results were encouraging up to the first 5 years, because the relapses are not yet so noticeable. It is at the end of 10 years, however, that the deluge of relapses can overwhelm even the most enthusiastic "chaulmoogrist," and in the end results in the abandonment of this ancient treatment. However, as noted elsewhere in this paper, I am personally acquainted with quite a few chaulmoogra negatives who are approaching the quartercentury mark without relapse, and they are not all "burnt-out" cases either. It should be remembered in this connection that in most countries using sulfones the critical ten-year period has yet to be reached.

#### CONCLUSIONS

1. There is still an urgent need for accurate surveys of relapses occurring among patients of both the lepromatous and the tuberculoid types who have been rendered "negative" by sulfone treatment. Such surveys should cover sufficient numbers of cases, observed over a long range of time extending to 10 years for most of them. The more such surveys are conducted in different countries, the better.

2. The results of the present survey and those reported by Erickson and Lowe imply that relapses would be greatly reduced if the treatment were to be continued among the released and discharged negatives. Mass treatment with the sulfones could be made into an effective health tool for the control of leprosy, provided this precaution is taken. Another practical implication of this finding is that, taken together with the wellknown slow action of the sulfones, a minimal period of 5 years of sustained treatment for all cases of the lepromatous type is indicated, whether such patients become clinically and bacteriologically negative or not.

### CONCLUSIONES

1. Existe todavía una necesidad urgente de estudios exactos de las recidivas observadas en leprosos de las formas tanto lepromatosa como tuberculoidea, que se han convertido en negativos con la sulfonoterapia. Esos estudios deben comprender números suficientes de casos, observados durante un largo período de tiempo que abarque 10 años para la mayor parte de ellos. Mientras más de tales estudios se lleven a cabo en países distintos, tanto mejor.

2. Los resultados de la encuesta actual y los presentados por Erickson y Lowe denotan que las recidivas disminuirían considerablemente si se continuara el tratamiento entre los negativos puestos en libertad y dados de alta. Con tal que se tome esta precaución, el tratamiento colectivo con las sulfonas podría convertirse en un instrumento sanitario eficaz para el dominio de la lepra. Otro corolario de este hallazgo es que, tomado junto con el conocido efecto lento de las sulfonas, se halla indicado un período mínimo de 5 años de tratamiento sostenido para todos los casos de la forma lepromatosa, ya se hayan vuelto o no esos enfermos clínica y bacteriológicamente negativos.