REPRINTED ARTICLES

Articles published elsewhere which are considered by the Editorial Board to be of special interest are, with permission reprinted in full, or in condensed form, or in free translation.

RELAPSE FOLLOWING APPARENT ARREST OF LEPROSY BY SULFONE THERAPY [1]

PAUL T. ERICKSON, M. D.
Clinical Director, U. S. Marine Hospital (National Leprosarium)
Carville, Louisiana

The tendency toward relapse following arrest of lepromatous leprosy by chaulmoogra oil therapy has been disappointingly high (1, 3). Although the sulfone drugs, promin and diasone, are generally considered superior to chaulmoogra oil for producing regression of specific leprous lesions and for arresting the disease, sufficient time has not elapsed for a comparative determination of the trend toward relapse (2). At least, up to the present, there have been no specific reports dealing with this subject in medical literature.

Of special interest, therefore, is the recent discovery at Carville of reactivation of the disease in six patients in whom the disease was supposedly arrested by sulfone treatment. Three of these patients showed a reappearance of leprosy bacilli in the skin without any other manifestations of the disease. Thus, they are termed subclinical relapses. The remainder presented, in addition, unquestionable leprous skin lesions or a true clinical relapse of the disease.

This paper reports these first cases of reactivation of leprosy following sulfone therapy and reviews the status of the sulfone-treated patients whom it has been possible to follow after apparent arrest of the disease. The criteria utilized for determination of arrest are described. The type, amount, and duration of treatment given to those patients in whom relapse occurred is compared to the average given to the entire group of patients who were followed. Finally, from the conclusions drawn, recommendations for the management of arrested cases of leprosy are discussed.

---

[1] Reprinted, verbatim, from *Public Health Reports 65* (1950) 1147-1157 by permission of the Surgeon General, U. S. Public Health Service.

CRITERIA FOR ARREST

The criteria by which the reactivated cases reported here were at one time classified as arrested cases are those routinely employed at Carville. Briefly, they are as follows for lepromatous cases:

1. Skin smears performed at monthly intervals must be negative for *Mycobacterium lepra* consecutively for a period of 1 year.
2. There must not be any evidence of clinical activity of the disease during the 1-year period of negativity.

The monthly skin smears, performed by scraping the edges of a small incision into the skin about 2 millimeters deep and staining the scrapings with an acid-fast stain, are taken by the bacteriologist from areas found positive for leprosy bacilli at the original examination. When the patient has shown negative skin scrapings from these areas for a period of 3 months, he is given a special examination by a board of physicians. A thorough inspection of the entire skin surface is made. Skin smears are taken at this examination from lesions which from their appearance suggest activity. Routine scrapings from the ear lobes, forehead, elbows, and nasal mucosa are also examined for acid-fast bacilli. If all the smears are negative, monthly smears are continued on the originally positive skin areas, and the special examination is repeated every 3 months. Whenever leprosy bacilli are found in any of the smears taken, even if the patient has had a long series of negative skin smears, he is required to begin anew on another series of tests when the first negative smear is obtained following a positive result. When, under this regime, a patient has been negative for a period of 1 year, a final examination is performed by the board of physicians. If all the smears are then negative and no evidence of activity has been present for 1 year, the disease is considered to be arrested.

The concentration of bacilli found in the skin and nasal smears are classified according to number as follows:

0 or negative .... No bacilli found.
1+ or rare ..... Less than 1 bacillus per microscopic field.[2]
2+ or few ..... 1-10 bacilli per microscopic field.
3+ or moderate .... 10-50 bacilli per microscopic field.
4+ or numerous .. More than 50 bacilli per microscopic field.

[2] Oil immersion 960X.

Although these criteria for arrest are not as rigid as those observed by most leprologists in other countries, it is felt that they give a fairly good indication of inactivity of the disease.

FOLLOW-UP

Sulfone therapy was first begun at Carville in March 1941. Three years later, in April 1944, the first sulfone-treated patients fulfilled the criteria for arrest of the disease. Since that date a total of 77 patients who had active disease when treatment was begun have had the disease arrested by sulfone drugs. Up to July 1, 1949, it has been possible, unfortunately, to keep only 33 of these patients under observation with routine clinical and laboratory examinations. These patients, all of the lepromatous type, form the basis for this report. The duration of follow-up varied from 6 months to 5 years.

It has been the practice at Carville to continue sulfone therapy for those patients who desire to continue treatment after apparent arrest of the disease. Thus, among the patients followed, 22 patients received promin or diasone either continuously or interruptedly after arrest. The majority of these received the drugs in smaller doses than that given during active treatment. Eleven patients received no antileprotic remedy after arrest of the disease.

The type of treatment and the average amount and duration of treatment given before the disease was arrested are summarized in table 1. Twenty-one patients each received an average of 2,840.5 gm. of promin for an average duration of 45 months; eight patients each received an average of 602.5 gm. of diasone for an average duration of 39 months; and four patients received, alternatingly, promin and diasone, an average of 393 gms. diasone and 1,262 gms. promin for an average duration of 49 months.

TABLE 1.—*Relapses found according to amount, duration, and type of sulfone treatment received by 33 patients prior to arrest of disease.*

Type of treatment	Number patients followed	Number and per cent relapses found	Average amount of treatment (gms.)	Average duration of treatment (months)
Promin	21	4 (19%)	2,840.5	45
Diasone	8	2 (25%)	602.5	39
Alternating	4	0		49
Promin			1,262.0	
Diasone			393.0	

Among the patients who received promin, four cases of relapse occurred—two clinical and two subclinical. One clinical and one subclinical relapse occurred among the patients who received diasone. Thus, a total of six relapses occurred among the 33 patients followed. The percentage of patients experiencing relapse was approximately the same in the promin-treated group (19 per cent) as in the diasone-treated group (25 per cent). There were no instances of relapse among the four patients receiving promin and diasone, alternatingly, but the number of patients followed is so small as to make this observation insignificant.

REPORT OF CASES

CASE 1. The patient, a white male, aged 27, began promin treatment June 3, 1942. At that time, he had had recognizable lesions of leprosy for 3 years, which consisted of infiltrated, circinate macules of the torso and upper extremities, diffuse thickening of the face, and scattered nodules over the face and extremities. The ulnar nerves were palpable and tender. There was loss of pain sensation over the ulnar side of the forearms, lower part of the legs, feet, and hands as well as over the specific skin lesions. Bacterioscopic examinations of skin and nasal mucous membrane were positive (3+). The lepromin test was negative.

During the course of treatment there occurred several febrile episodes associated with erythema nodosum and neuritis. At one time (1944) a left iridocyclitis complicated the usual type of reaction. The specific skin and mucous membrane lesions underwent resolution in the usual time. The criteria for arrest of the disease were fulfilled on July 18, 1945, after the patient had received 3,402.5 gm. promin intravenously for a period of 3 years, 2 months.

The patient was discharged from the hospital after arrest of the disease and treatment was discontinued. He was well until December 1947 when red spots began to appear over the body. This was 29 months following arrest of the disease. He was readmitted to Carville April 20, 1948. Scattered plaques and macules, varying in color from coral to tan, were found over the torso and extremities. An ulcerated area was found on the right side of the nasal septum. Bacterioscopic examinations of skin and nasal mucous membrane were positive (2+ and 1+ respectively). Regression of lesions occurred with the resumption of promin treatment.

CASE 2. The patient, a white male, aged 35, began promin treatment in July 1942. At that time he had had recognizable lesions of leprosy for 7 years, consisting of diffuse thickening of the face, brow, and ears; medium-sized, copper-colored, infiltrated macules scattered over the face, extremities, and torso; thickened ulnar, peroneal, and great auricular nerves; moderate interosseous atrophy of hands, extensive anesthesia of extremities, and a weak right ankle. Bacterioscopic examinations of skin and mucous membrane were positive (3+). The lepromin test was negative.

During the course of treatment, erythema nodosum, neuritis, and fever occurred at infrequent intervals. Otherwise, response to treatment was that usually experienced. The criteria for arrest of the disease were fulfilled on

October 9, 1946, after the patient had received 3,685.5 gm. of promin intravenously for a period of 4 years 3 months.

The patient was discharged from the hospital after arrest of the disease; treatment was discontinued. He had his first bacteriologic check-up 17 months later (February 1948) and acid-fast bacilli were found in the skin. In September 1948 he developed chills, fever, general weakness, and skin lesions on the chest. In January 1949 he returned to Carville for further treatment. There were present at that time a rather marked infiltration of the face, brow, and ears; many copper-colored, infiltrated macules scattered over the chest, back, buttocks, and extremities; extensive anesthesia of extremities; marked atrophy of the intrinsic muscles of the left hand with contracture; and thickening of the ulnar, peroneal, and great auricular nerves. Regression of skin and mucous membrane lesions occurred on promacetin treatment.

CASE 3. The patient, a white male, aged 60, began promin treatment on October 1, 1943. At that time he had had recognizable leprous lesions for 5 years, consisting of a generalized eruption of large, infiltrated, red, raised macules on the extremities and body; diffuse thickening of the face, brow, ears, hands, lower portion of legs, and feet; enlarged, tender ulnar nerves; slight atrophy of the intrinsic muscles of hands; extensive anesthesia, stocking and glove-like, including knees and elbows; and generalized adenopathy. Bacterioscopic examinations of skin and mucous membranes were positive (4+). The lepromin test was negative.

During the course of treatment a number of febrile episodes with erythema nodosum occurred between August 30, 1944 and December 1, 1944. Otherwise, response to treatment was uneventful and skin lesions resolved in due time. The criteria for arrest were fulfilled on February 3, 1948, after the patient had received 3,285.5 gm. of promin intravenously for a period of 4 years 4 months.

The patient was discharged from the hospital after arrest of the disease; treatment was discontinued. He returned to Carville on July 29, 1948, for treatment of infected trophic ulcers of the feet. Bacterioscopic examinations were positive (skin 1+ and nasal mucosa 1+), although there were no visible or palpable skin lesions.

CASE 4. The patient, a white male, aged 53, began promin treatment in July 1942. At that time he had had recognizable leprous lesions for 5 years, consisting of multiple, pea-sized nodules over the cheeks and forehead, both arms, and both legs; diffuse thickening of the skin of the face and extremities; thickened ulnar and peroneal nerves; loss of pain sensation of entire left upper extremity, dorsum of right hand, and both legs; moderate injection of both eyes from leprous iridocyclitis; and ulceration of the nasal mucous membrane. Bacterioscopic examinations of the skin and nasal mucous membrane were positive (4+). The lepromin test was negative.

Improvement on promin therapy was slow but definite. There were occasional episodes of erythema nodosum with fever. The criteria for arrest were fulfilled on March 31, 1947, after the patient had received 1,441 gm. of promin intravenously for a period of 4 years 9 months.

The patient was discharged from the hospital after arrest of the disease and treatment was discontinued. A personal communication from a leprosarium in Mexico City, Mexico, during April 1948 gave information that the patient had recently been examined there and found to show positive skin smears.

CASE 5. The patient, a white male, aged 60, began diasone treatment August 9, 1943. At that time he had had recognizable lesions of leprosy for an unknown duration, consisting of diffuse thickening of the face, brow, and ears; enlargement of the ulnar nerves; and scattered areas of anesthesia of the upper part of both arms. Bacterioscopic examinations of skin and nasal mucous membrane were positive (3+). The lepromin test was negative.

During the course of treatment there were occasional febrile episodes associated with erythema nodosum. Neuritis occurred frequently. Clinical improvement was gradual and the criteria for arrest of the disease were fulfilled November 15, 1946, after the patient had received 575 gm. of diasone orally for a period of 3 years 3 months.

The patient was discharged from the hospital after arrest of the disease; treatment was discontinued. He had his first follow-up examination approximately 3 years later. Skin smears from the right ear and right brow were positive (2+) for leprosy bacilli and both ear lobes presented slight infiltration and erythema.

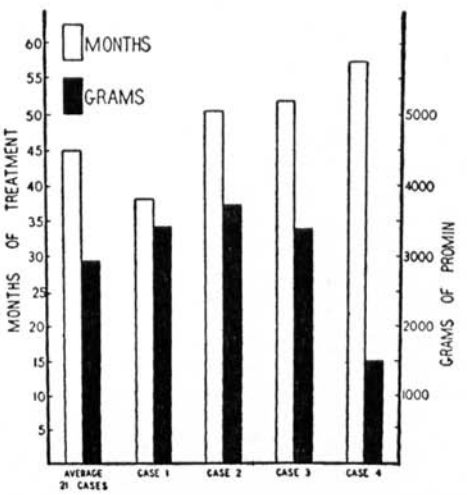
CASE 6. The patient, a Negro male, aged 35, began diasone treatment on November 11, 1944. At that time he had had recognizable leprous lesions for 4 years, consisting of pea-sized nodules of the face and ears; patches of infiltrated skin over the back; thickened ulnar and peroneal nerves; impairment of pain sensation over the legs, feet, and hands; enlarged femoral and inguinal glands; and ulceration of the nasal mucous membrane. Bacterioscopic examinations of the skin and nasal mucous membrane were positive (4+). The lepromin test was not made.

Response to diasone treatment was rapid. Slight febrile reactions with erythema nodosum occurred occasionally. The criteria for arrest of the disease were fulfilled May 31, 1946, after the patient had received 376.5 gm. of diasone for a period of 18 months.

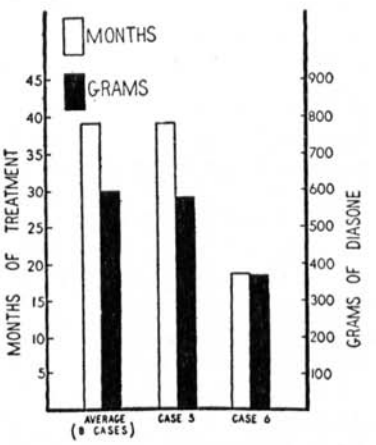
After arrest of the disease, the patient remained in the hospital and was continued on 1.0 gm. of diasone daily. In December 1947 (18 months after arrest and after an additional 474 gm. of diasone had been administered, at the regular 6-month check-up examination performed on all arrested cases remaining in the hospital, leprosy bacilli (1+) were found in the skin smear from the ear lobes. There were no evidences of infiltration, thickening, nor of other clinical activity. The nasal smear was negative as were skin smears from other areas of the body. Bacilli (1+) continued to be present in the ear lobes despite treatment (488 gm. diasone) until August 1949. No other evidences of activity of the disease were found subsequent to fulfillment of the criteria for arrest nor after reactivation had occurred.

Figure 1 shows the relationship between the average amount and duration of treatment received by the group of patients treated with promin before arrest of the disease was accomplished and that received individually by the relapsed cases in the promin-treated group. Figure 2 shows the same data for the diasone-treated group. The amount and duration of treatment received by the relapsed cases in both groups compares favorably with the average amount of treatment received by the nonrelapsed cases in each group except in the instances of cases 4 and 6. It

would appear from this analysis that relapse of the disease did not occur from insufficient treatment except possibly in cases 4 and 6. Case 4 received a relatively small amount of promin over a relatively long period of time before arrest of the disease was accomplished. Case 6 received a relatively small amount of diasone over a relatively short period of time.



TEXT-FIG. 1. Comparison of the average amount of promin and duration of treatment received by the nonrelapsed promin-treated patients with that received individually by the relapsed promin-treated patients. Black column represents amount of promin received in grams. White column represents duration of treatment in months.



TEXT-FIG. 2. Comparison of the average amount of diasone and duration of treatment received by the nonrelapsed diasone-treated patients with that received individually by the relapsed diasone-treated patients. Black column represents amount of diasone received in grams. White column represents duration of treatment in months.

A most important factor influencing the probability of relapse appeared to be the discontinuation of treatment after apparent arrest of the disease had occurred. Patients who did not receive sulfone therapy following arrest are designated group A and those who received such therapy, group B. Table 2 lists the frequency of relapse as it occurred in these two groups during yearly periods of observation. True clinical relapses, of which there were three, occurred only in group A, the group that received no treatment after arrest. These relapses did not occur until after 2 to 3 years following arrest of the disease. Subclinical relapses occurred in both groups. Two occurred in group A within the first year following arrest and one in group B 18

months following arrest. The latter is case 6 who received a relatively small amount of diasone before fulfillment of the criteria for arrest.

Thus, the trend of group A patients indicates that the probability of relapse is markedly increased if sulfone therapy is discontinued after an apparent arrest of the disease. Relapse that has so far occurred among 11 arrested patients (group A) who received no sulfone therapy and were followed from 6 months to 4 years is 45 per cent. This percentage of relapse is tenfold greater than that of the 4.5 per cent experienced among 22 arrested patients (group B) continued on sulfone therapy and followed from 6 months to 5 years.

TABLE 2.—*Relapses found in the 33 group A and group B arrested patients by period of follow-up in years.*

Period of follow-up (years)	Number arrested patients followed		Number and per cent relapsed patients	
	A[1]	B[2]	A[1]	B[2]
½ — 1	4	4	2[3]	0
1 — 2	1	3	0	1[3]
2 — 3	5	3	3[4]	0
3 — 4	1	10	0	0
4 — 5	0	2	0	0
Total	11	22	5 (45%)	1 (4.5%)

[1] Patients not receiving sulfones after arrest.
[2] Patients receiving sulfones after arrest.
[3] Subclinical relapse.
[4] Clinical relapse.

Table 2 shows that on an average a larger proportion of group B patients were followed for longer periods of time than were group A patients. Thus, group B patients were afforded a greater opportunity to relapse. Calculating the risk of relapse on a patient-years experience basis as set forth in table 3, however, accentuates even more the divergence of the probability of relapse between the two groups. On this basis, which has greater accuracy for it takes into consideration the time interval, the risk of relapse for group A was 24.4 relapses per 100 patient-years experience, while for group B it was only 1.7 relapses per 100 patient-years experience, or a trend fourteenfold greater for group A to relapse than group B.

TABLE 3.—*Relapses found in 33 group A and group B arrested patients on the basis of patient-years experience.*

Period of follow-up (years)	Average duration of follow-up (years)	Number patients observed		Number patient-years experience		Number and per cent of relapses	
		A	B	A	B	A	B
½ — 1	0.75	4	4	3	3	2	0
1 — 2	1.50	1	3	1.5	4.5	0	1
2 — 3	2.50	5	3	12.5	7.5	3	0
3 — 4	3.50	1	10	3.5	35.0	0	0
4 — 5	4.50	0	2	0.0	9.0	0	0
Total		11	22	20.5	59.0	5 (24.4%)	1 (1.7%)

DISCUSSION

The occurrence of relapse following apparent arrest of lepromatous leprosy under treatment with sulfones, undoubtedly, has been anticipated even by the most enthusiastic supporters of sulfone therapy. The fact that relapses have occurred does not brand the sulfones as failures in the therapy of leprosy. In fact, it detracts very little, if any, from the reported value of these drugs in this relentless disease. Their ability to produce regression of leprous lesions and to keep the ravages of the disease in check cannot be discounted.

Since the problem of finding leprosy bacilli in resolving surface lesions becomes a matter of progressively decreasing chance, it is probable that some patients may be declared negative prematurely. From this, it can be argued, that if a negative patient is subsequently found to have a positive skin smear in the absence of clear clinical evidence of reactivation, such a finding is merely a chance interruption of a false negative period rather than a relapse of the disease. In this report the occurrence of a positive skin smear without other manifestations of the disease has been termed a "subclinical relapse" on evidence obtained from case 2. This case showed a positive skin smear 17 months after the disease was considered arrested. Eight months later skin lesions developed and a true clinical relapse occurred. It seems logical to consider the period prior to development of skin lesions and subsequent to the finding of a positive smear as a subclinical relapse of the disease rather than a chance interruption of a false negative period.

The slow disappearance of leprosy bacilli from the skin of most patients under active treatment and the inability to obtain consistent negative skin smears from some, although clinically the response has been excellent, have led to the belief that the sulfones are suppressive or bacteriostatic rather than bactericidal in their action. Now that relapses of the disease have been experienced, added support is given to this belief. Temporary partial or complete natural remissions of the disease, undoubtedly, also play a role where the disappearance of clinical lesions and of bacilli from the skin are accelerated beyond expectation. Complete spontaneous remissions or arrests of far advanced nodular lepromatous cases of leprosy, such as those under consideration in this report, however, are rare occurrences.

Case 6 is, perhaps, the most interesting and illustrative of this suppressive action and the role of natural remission. The nodular and infiltrative lesions shown by this patient receded rapidly on diasone therapy. After 18 months of treatment he fulfilled the criteria for arrest of the disease. Treatment was taken regularly following apparent arrest by the same dosage as during active treatment. After another 18 months of treatment, a 1+ concentration of organisms was recovered from the right ear lobe. There were no visible skin lesions and the nasal smear was negative. After continued regular treatment for another 2 years no skin or mucous membrane lesions developed. The right ear lobe continued to show leprosy bacilli (1+) on monthly examinations. This patient at present has had a total of 5 years' treatment. There has been no clinical evidence of the disease for 4 years and bacteriologic examinations are still positive. It is believed that the sulfones, aided by the forces of natural remission, accounted for the early improvement. The suppressive action of the sulfones has not been of sufficient intensity to prevent the return of organisms, but it has prevented the formation of clinical lesions. The question of "chance interruption" is ruled out by the failure to recover organisms on numerous repeated attempts during a period of 30 months, followed by an easy consistent demonstration of organisms after that period.

The figures given for the probability of relapse are tentative and, in the final analysis, may not be representative of what the true incidence of relapse eventually will be. Since the number of patients followed is small, a great deal of significance cannot be placed on the statistical results obtained. Also, the duration of follow-up has been short in some instances. A factor of

selection may have entered into the calculations particularly with reference to the patients representing clinical relapse. Two of these patients had been discharged from the hospital and returned when skin lesions appeared. Since patients who develop visible evidences of the disease are, undoubtedly, more likely to return for examination than those who do not develop them, it may be that the three cases of clinical relapse here reported are the only ones that have developed among all of the patients so far having their disease arrested on the sulfones. Should this be the case the probability of clinical relapse would be much less at the present stage of follow-up than is indicated by this report. Whether or not the probability of relapse after remissions from sulfones will be as great as that (a great majority in from 3 to 5 years) experienced for remissions from chaulmoogra oil remains to be seen.

Table 2 and 3, although based on small figures, are clear expositions of evidence that relapses are not as likely to occur when sulfone therapy is continued indefinitely. Because of this evidence it is advocated that all cases of lepromatous leprosy following apparent arrest of the disease be continued on sulfone treatment. Also, experience has shown that if treatment is continued, relapses can be prevented even if the dosage of the drug employed is materially reduced. Toxic effects, therefore, need not be especially feared. In the group of patients here reported the dosage was generally reduced to about one-third of that employed during active treatment.

CONCLUSIONS AND RECOMMENDATIONS

As has been anticipated, relapses may occur following the arrest of lepromatous leprosy after sulfone therapy.

Over a 5-year period in which the follow-up varied from 6 months to 5 years after arrest of lepromatous leprosy on sulfone therapy, relapse rates of 45 per cent for patients not continued on sulfones and 4.5 per cent for those continued on treatment were experienced. When the probability of relapse was based on patient-years experience, the respective risks of relapse were 24.4 and 1.7 per 100 patient-years experience. Because of obvious selection factors and the limited material available for study, these figures are not claimed to represent true incidences of relapse. They merely indicate a trend.

A comparison of the risk of relapse for the two groups of patients studied strongly indicates that the incidence of relapse

can be markedly lowered if sulfone treatment is continued after arrest.

The occurence of relapse following arrest of the disease when the sulfone drugs are discontinued indicates that the sulfones are suppressive or bacteriostatic, rather than bacteriocidal, in their action. The persistence of leprosy bacilli (1+) in the skin of patients under active treatment for long periods of time without the reappearance of clinically visible lesions gives added evidence to this belief.

Evidence that the incidence of relapse can be effectively lowered by continuation of sulfone therapy in reduced dosage calls for a recommendation that treatment be continued indefinitely in such a manner for arrested cases.

REFERENCES

1. COCHRANE, R. G. Practical Textbook of Leprosy. New York, Oxford University Press, 1947, p. 129.
2. JOHANSEN, F. A. and ERICKSON, P. T. Studies on the therapy of leprosy. Proc. 4th Internat. Cong. Trop. Med. and Malaria **1** (1948) 365.
3. WADE, H. W. and LARA, C. B. Studies on negative lepers. III. The problem of relapses. J. Philippine Med. Assoc. **7** (1927) 115-122.