Much success has been reported in the treatment of leprosy within the past seven years from those countries where the sulfone drugs—promin, diasone and promizole—have been used (1-6). Similarly encouraging therapeutic results have been reported within recent months for another related sulfone called sulfetrone (7). All of these reports seem to indicate that, thus far, the chief value of the sulfones lies in their salutary therapeutic effect on lesions of the skin and mucous membranes. They appear to be able slowly to produce recessive changes in, and healing of, leprous nodules and infiltrations; to cause disinfection, granulation and healing of leprous and trophic ulcerations; and gradually to eliminate the leprosy bacilli from such lesions. It is not unreasonable, therefore, to expect that such concomitant lesions as occur in the bones and nerves in leprosy would also in some degree respond to the healing influence of these drugs.

What value the sulfones may have in preventing, arresting or healing the bone lesions has not as yet been sufficiently explored. This state of affairs is not due to a lack of scientific interest in this subject on the part of leprologists; it is due to a lack of adequate scientific observation dependent upon the nature of an extremely chronic disease—a disease which is slow in its development and slow in its response to treatment.

Apart from the occasional lesions presumably due to the direct action of Mycobacterium leprae, bone changes in leprosy are more or less entirely dependent on neurotrophic disorders which are secondary to nerve involvement (8, 9). They manifest themselves mainly in the form of atrophic absorption of the small bones of the extremities. Because of the close association be-
tween the bone changes and nerve lesions, a study of one type of lesion must of necessity include the other.

Neural involvement in leprosy, as is true of nearly all other pathological processes associated with the disease, is slow in its evolution; bone involvement, comparatively speaking, is even slower in its appearance. Leprous neuritis or infection of nerves must be of sufficiently long duration and of an advanced stage, with degeneration and fibrosis of nerve fibers, before bone absorption takes place. The gradual slow injury to motor and sensory neurones resulting from leprous infiltrations and swellings, with or without permanent damage, manifest themselves weeks, months and perhaps even years later in muscular atrophy, contractures and bone changes.

Any treatment which would heal or abort the nerve lesions, it is believed, would also tend to prevent and arrest the bone absorption. It is to be expected that response to treatment would be equally as slow as the original evolution of the lesions; it is also expected that loss of function or tissue due to permanent injury of nerves would not be restored. All of this suggests that any evaluation of the effects of treatment on atrophic bone absorption must of necessity extend into years and decades rather than weeks or months. It explains our present lack of data on this particular phase of treatment with the sulfones.

It is the purpose of this paper to report the bone changes observed in patients on sulfone therapy concerning whom there is available roentgenologic follow-up for a period of five years. It is admitted that this period of observation is entirely too short to permit of any final conclusions. Our findings, however, may provide certain partial answers to the question of what happens to leprous bone changes during sulfone therapy.

CLINICAL MATERIAL AND PROCEDURE

This study concerns 82 patients under treatment with promin, diason or promizole, of whom there are available x-ray pictures of the bones of hands and feet made over a period of approximately five years. Due to the scarcity of x-ray film during the war period and to the fact that this study was not premeditated, the majority of patients have had only two sets of roentgenological examinations, including an original and a five-year follow-up. In a few instances original films are not available for both hands and feet, one or the other having been omitted.

Of this group, 75 cases (91 per cent) were of the lepros-
matous type, while only 7 cases (9 per cent) were of the purely neural type. However, of the lepromatous patients 63 had some neural element, the involvement varying from slight to extensive; they (77 per cent of the total) were of the "mixed" class. Consequently a total of 70 patients (85 per cent) had a neural element and were fit subjects for a long-range study of bone changes (Table 1).

TABLE 1.—Duration of sulphone treatment and type of leprosy involved in Group I and Group II patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration of treatment (years)</th>
<th>Lepromatous</th>
<th>Mixed</th>
<th>Neural</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>I</td>
<td>More than 5</td>
<td>2</td>
<td>9.6</td>
<td>19</td>
<td>90.4</td>
</tr>
<tr>
<td>II</td>
<td>4 to 5</td>
<td>3</td>
<td>16.4</td>
<td>7</td>
<td>34.2</td>
</tr>
<tr>
<td></td>
<td>3 to 4</td>
<td>5</td>
<td>16.4</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>1½ to 3</td>
<td>2</td>
<td>16.4</td>
<td>7</td>
<td>34.2</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>12</td>
<td>14.6</td>
<td>63</td>
<td>76.8</td>
</tr>
</tbody>
</table>

Of the entire group, 21 patients (26 per cent) were put under sulphone treatment prior to the original roentgenologic studies. With the remaining 61 patients (74 per cent), treatment began anywhere from the time of the original x-ray examination up to three and one-half years afterward. Two comparable groups, Nos. I and II (Table 1), can thus be distinguished for the purpose of discussion, between which the only significant difference is the length of treatment involved in relation to the time when roentgenologic studies were first performed. The patients of Group I were treated for more than five years, and those of Group II for from one and one-half to five years. There was a slightly higher percentage of pure lepromatous cases in Group II, which may have an influence on results as a factor of selection.

Fifty-two patients received promin, 28 diason and 2 promizole. Vitamins, iron, liver and calcium preparations were administered routinely as indicated. Treatment when once begun was continuous and adequate in all but a very few instances. It was given according to the routine method used at Carville (see references). The original films, any intervening ones, and the last ones were compared to determine what bone changes had occurred during the period of observation.

The most frequent finding, which lent itself quite well toward determining the degree of involvement and also the degree
of advance, increase or retrogression, was atrophic bone absorption. Changes in the tufts of the terminal phalanges, together with slight concentric bone atrophy of the shafts of the phalanges (usually the proximal row of phalanges in the feet and the terminal row in the hands), has been termed slight involvement; marked narrowing of the shafts of the phalanges (associated occasionally, in the case of the feet, with slight atrophy of the heads and shafts of the metatarsals) without any other destructive changes, is called moderate involvement; and almost total or total loss of phalanges, marked concentric atrophy with destructive changes, or definite changes in metatarsals, metacarpals, tarsal or carpal bones, is called extensive involvement. Appraisal of the degree of retrogression, advance or increase of involvement has been based as nearly as possible on these three categories.

The only other fairly frequent condition which could be used for purposes of comparison is definite bone-cyst formation. Classification as to degree of involvement or increase in involvement of this lesion has been more difficult. In general, it has been based on the number of cysts and number of bones affected. Destructive changes when due to cysts have been taken into consideration.

No attempt has been made to consider diffuse leprous osteitis, degrees of rarefaction, periostitis, arthritis, necrosis, osteomyelitis, enlarged nutrient canals, or joint involvement, except only as these affected the entire picture of the two main elements used for comparative purposes.

Since neural involvement precedes bone changes in the majority of cases, a clinical history and examination was obtained on each patient and correlated with previous findings in this regard.

ROENTGENOLOGIC AND CLINICAL FINDINGS

The findings relative to the two main bone changes used for comparative purposes for the two groups of patients, they classified according to amount of sulfone treatment received, are set forth in Table 2. The percentages of patients showing bone changes in the feet at the outset were the same for the two groups. Group II showed less involvement of the hands by only 10 per cent. The two groups were therefore fairly comparable as far as original extent of bone changes is concerned.
TABLE 2.—Bone changes observed in the hands and feet in patients of Group I and Group II over a five-year period.

<table>
<thead>
<tr>
<th>Retrospection or improvement of lesions</th>
<th>Group I a</th>
<th>Group I b</th>
<th>Group II a</th>
<th>Group II b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Absorption</td>
<td>Cyst Formation</td>
<td>Bone Absorption</td>
<td>Cyst Formation</td>
<td></td>
</tr>
<tr>
<td>No lesions present</td>
<td>6 (30%)</td>
<td>18 (90%)</td>
<td>16 (29%)</td>
<td>50 (91%)</td>
</tr>
<tr>
<td>Lesions stationary</td>
<td>9 (45%)</td>
<td>0</td>
<td>19 (38%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Slight increase</td>
<td>5 (25%)</td>
<td>0</td>
<td>6 (11%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Moderate increase</td>
<td>0</td>
<td>0</td>
<td>8 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Extensive increase</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New lesions appeared</td>
<td>0</td>
<td>1 (5%)</td>
<td>4 (7%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Improved</td>
<td>0</td>
<td>1 (5%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

**FEET**

<table>
<thead>
<tr>
<th></th>
<th>Group I a</th>
<th>Group I b</th>
<th>Group II a</th>
<th>Group II b</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesions present</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lesions stationary</td>
<td>1 (45%)</td>
<td>0</td>
<td>19 (38%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Slight increase</td>
<td>6 (25%)</td>
<td>0</td>
<td>6 (11%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Moderate increase</td>
<td>0</td>
<td>8 (14%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extensive increase</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New lesions appeared</td>
<td>0</td>
<td>1 (5%)</td>
<td>4 (7%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Improved</td>
<td>0</td>
<td>1 (5%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

**HANDS**

<table>
<thead>
<tr>
<th></th>
<th>Group I a</th>
<th>Group I b</th>
<th>Group II a</th>
<th>Group II b</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesions present</td>
<td>13 (72%)</td>
<td>14 (77%)</td>
<td>39 (59%)</td>
<td>41 (87%)</td>
</tr>
<tr>
<td>Lesions stationary</td>
<td>4 (22%)</td>
<td>1 (6%)</td>
<td>6 (11%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Slight increase</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate increase</td>
<td>0</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Extensive increase</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New lesions appeared</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Improved</td>
<td>0</td>
<td>3 (17%)</td>
<td>0</td>
<td>5 (11%)</td>
</tr>
</tbody>
</table>

a Of this group of 21 patients, 1 had no previous film of the feet for comparison, and 3 lacked previous films of the hands.

b Of this group of 61 patients, 6 had no previous film of the feet for comparison, and 14 lacked previous films of the hands.

Atrophic bone absorption of the feet remained stationary in 45 per cent of Group I and in only 35 per cent of Group II; it became worse in only 25 per cent of Group I as compared with 36 per cent of Group II. The same figures for the involvement of hands were, for Group I: stationary 22 per cent, worse 6 per cent; for Group II: stationary 11 per cent, worse 6 per cent. Cysts of bones appeared to heal very well in both groups, though to a greater extent in Group I. Cysts appeared in the
bones of the feet during treatment in three cases which had received inadequate treatment because of intolerance for adequate doses. The fact that bone cysts have been observed to heal quite rapidly suggests that they may be true lepromata of bone as intimated by Faget and Mayoral, rather than evidence of extensive bone decalcification or rarefaction.

Clinical summaries of the patients of the two groups in whom retrogression or improvement of bone lesions took place have been tabulated and reduced prints of representative early and late films prepared.*

Here only four of these cases will be mentioned.

The first case presented is a male aged 32 years, the disease of 15 years duration, "mixed," on promin treatment since January 1942. The original film (hands only; Fig. 1) was made in April 1945; a recent one (Fig. 2) shows improvement of bone texture and extensive healing of cysts, illustrating the finding that cysts respond well.

The second case, a male aged 24 years, duration 10 years, "mixed," on promin since August 1942. First film (see Fig. 3, feet) in January 1943. A recent one (Fig. 4) shows slight increase of bone absorption, but healing of an area of necrosis, again illustrating the finding that lesions probably due to direct action of bacilli or secondary infection usually improve under treatment, while those due to existing nerve lesions may grow worse.

The third case, a female aged 22 years, duration 9 years, "mixed," on diason since June 1944 and promin since October 1946. First film made in January 1942; subsequent films, up to May, 1944, showed gradual increase in cyst formation; one made then (hands only; Fig. 5) shows the height of involvement. A recent one (Fig. 6) shows extensive healing of cysts and slight increase of bone absorption.

The fourth case, a female aged 48 years, duration 13 years, "mixed," on diason since July 1944. First film (Fig. 7, feet) made in February 1943; a recent one (Fig. 8) shows definite bone absorption in the interim, which may have occurred before treatment was started.

In the historical and clinical review of neural signs and symptoms (Table 3) some evidence was accumulated which indicates that those patients who took treatment throughout the entire five-year period (Group I) showed more improvement in neural lesions than those who had less treatment (Group II). While only one neural condition became worse or appeared among patients of Group I, 19 of them became worse (or appeared among those of Group II. Patients who developed neural signs or symptoms while taking sulfone have been excluded if later improvement took place. It is thought that the mechanism involved in the improvement noted in objective and subjective neural findings is probably a release of pressure upon the

* See Footnote 1.
sensory and motor neurones due to a reduction of swelling within the nerve sheath, rather than to a regrowth of axis fibers.

Table 3.—Summary of neural signs and symptoms shown by the patients in Groups I and II and probable response to treatment.

<table>
<thead>
<tr>
<th>Neural signs and symptoms</th>
<th>GROUP I (21 PATIENTS)</th>
<th>GROUP II (61 PATIENTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Improved during</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sulfone</td>
</tr>
<tr>
<td>Slight loss of sensation</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Marked loss of sensation</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Painful enlarged nerves</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Muscular atrophy</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Contractures</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Absorption a</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Foot drop or ankle weakness</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Marked loss of sensation</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Painful enlarged nerves</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Muscular atrophy</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>Contractures</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Absorption a</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Foot drop or ankle weakness</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

a By gross examination.

DISCUSSION

One of the most recent and extensive clinical and roentgenologic reviews of bone changes in leprosy is that by Faget and Mayoral (8). In an exhaustive study of 505 cases at the National Leprosarium these investigators, in addition to confirming the existence of bone lesions in leprosy previously
described by others (9, 10), made it clear that certain of them correspond to certain categories of the disease.

It is the opinion now, for instance, that lepromatous leprosy, if relatively free from neural involvement, is usually free from bone lesions except those possibly due to the direct action of M. leprae. Such lesions are cysts and osteomyelitis. Enlarged nutrient foramina due to vascular disturbances also occur as do osteomyelitis and periostitis from secondary infections. The most intense and important bone changes occur in the pure neural type, where the degenerative effects from nerve involvement cause secondary bone absorption of neurotrophic nature. In mixed cases are seen bone changes common to both the lepromatous and neural types.

It appears, then, that the important consideration is the nerve lesion, and that in order to arrest bone changes—except in the rather rare, probably true lepromatous involvement—the leprous nerve process must be aborted. Existing permanent injury or degeneration of nerves cannot be corrected, and bone changes may occur long after the time of that injury.

Although the figures given are not significant because of the small numbers of patients concerned, they indicate that sulfone treatment probably produces a restraint on further progression of atrophic bone absorption. The degree of this restraint depends in a large measure on the extent of neural involvement prior to treatment. If the nerve changes are marked, bone changes are liable to continue; if involvement of the nerves is slight or early, arrest of the process in the bones is probable. Early treatment is therefore of primary importance with a view to preventing extensive neural involvement and secondary bone changes.

Bone cysts and osteitis or osteomyelitis, presumably of leprotic origin, have been noted to heal more rapidly under sulfone therapy than that observed in our experience as due to spontaneous healing. The same can be said for necrosis of bone secondary to infected trophic ulcers. Two almost identical cases of local rarefying osteitis of the head of the astragalus, appearing shortly after inception of sulfone treatment, later healed within a relatively short time. These cases are not included in the comparison groups because of lack of five-year follow-up studies. Improvement in bone texture or rarefaction and in diffuse rarefying osteitis, also, does take place under sulfone therapy.

Another bit of evidence that sulfone treatment has been
beneficial is indicated by the proportion of true lepromatous cases found in each group. Group II contains a slightly higher percentage of such cases than Group I. Because of this factor of selection, less bone involvement and less increase in bone changes would be expected in Group II than in Group I providing sulfone treatment has no effect. The results obtained are to the contrary, and in favor of sulfone treatment.

Spontaneous arrest of bone changes, such as atrophic absorption and spontaneous healing of cysts, undoubtedly occurs as does spontaneous regression in skin lesions. To what extent such a process has occurred in this study it is difficult to determine. The fact, however, that the shorter-treatment group did not do as well as the group treated for more than five years suggests that the lack of retrogression of bone changes in this group was not entirely due to spontaneous arrest.

To give a definite answer as to the value of the sulfones in bone lesions of leprosy, a more prolonged study of a larger group of patients is necessary. Any follow-up period of less than ten years is considered insufficient for determining the true probability and degree of prevention or arrest.

CONCLUSIONS

Observation of bone changes in leprosy over a five-year period in a group of patients treated adequately with sulfone drugs indicates that lesions of bones presumably due to the direct action of M. leprae, such as cysts, heal; and that a restraint on further progression of atrophic bone absorption, secondary to neural involvement, probably occurs.

Where extensive neural involvement is present prior to treatment, secondary bone changes are liable to increase in severity.

The apparent relatively rapid healing of bone cysts under sulfone treatment suggests that they may be true lepromata of bone.

Studies of bone changes during treatment of leprosy must of necessity be of long duration because of the usual slow evolution of such lesions and the slow response of most leprous lesions to treatment.

The prevention of bone changes in leprosy through early treatment with sulfones is an apparent possibility.

Further study of bone changes during sulfone therapy, in a larger group of patients over a longer period of time, correlated with accurate observations on nerve lesions, is recommended as necessary before final conclusions can be drawn.
ACKNOWLEDGMENTS

Acknowledgment is made of the assistance provided by Dr. Paul A. McIlhenny, Consultant in Orthopedic Surgery, U. S. Marine Hospital, Carville, Louisiana, and Dr. A. Mayoral, Roentgenologist, U. S. Marine Hospital, New Orleans, Louisiana, for the interpretation of x-ray films, helpful suggestions, and critical review; and to Sister Hilary Ross for preparing photographs.

REFERENCES


DESCRIPTION OF PLATES

PLATE (3)

Figs. 1 and 2. Roentgenographs of hands, taken April 1943 and December 1947, respectively, showing healing of cysts. (A case of treatment-group 1.)
FIGS. 3 AND 4. Films of feet, taken in January 1943 and November 1947, respectively, showing healing of an area of necrosis and slight increase of bone absorption. (A case of treatment-group I.)
PLATE (6)

FIGS. 7 AND 8. Films of feet, taken in February 1943 and November 1947, respectively, showing the appearance of bone absorption. (A treatment-group II case.)