PRESENT STATUS OF PROMIN TREATMENT IN LEPROSY*

by

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Clinical improvement of patients suffering from leprosy and treated with intravenous promin has already been reported (1,2). The purpose of this discussion is to bring up to date the data pertaining to the value of promin in the treatment of leprosy.

Clinical Material. This report concerns 177 patients suffering from leprosy, who have received a total of 268,836 Grams of promin intravenously in daily doses averaging from 2-5 Grams per day, depending largely on the weight of the patient. The amount of promin reported is more than twice the amount used in the last report on the subject (2). Of these 177 patients, 137 (76.8%) are either still taking the drug or have stopped as discharged (arrested) cases. The remaining 40 cases (23.2%) have been discontinued for the following reasons:

Absconded from the Leprosarium (12)	6.77%
Requested oral sulfone treatment (7)	3.95%
Pre-existing renal insufficiency (6)	3.38%
Erythema nodosum (febrile attack) (5)	2.82%
Hypertension (2)	1.13%
Exfoliative dermatitis (1)	0.67%
Angioneurotic edema (1)	0.67%
Lymphadenopathy (febrile attack) (1)	0.67%
Died of intestinal tuberculosis (2)	1.13%
Died of pulmonary tuberculosis (1)	0.67%
Died of carcinoma of pancreas (1)	0.67%
Died of leprous laryngitis (after small doses of promin for a short time)	0.67%
Total discontinued (40)	23.20%

Of the remaining 137 patients, who have been treated regularly, 75.3 per cent (103) are predominantly lepromatous in type, 21.8 per cent (3) are frankly mixed in type with extensive lepromatous and neural changes, while only 2.9 per cent (4) are of the neural type. While the four neural type patients are doing well on promin treatment, the reason that so few of that type have been treated

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has been the desire to treat largely cases that are frankly lepromatous, usually of rather advanced degree, cases in which the prognosis without treatment would be poor.

Procedure: For the past two years, injections of promin have been given daily for two weeks, followed by a period of one week during which there are no injections, but a complete blood count and urinalysis are made, after which the drug is given for another two weeks, etc. Injections have been given for six days a week. Since each patient should receive six injections a week, two-thirds of the weeks, he should get approximately 207 injections a year. Injections are not started unless the red blood cells are 3,500,000 or more and the drug is stopped if the red blood cells fall below 3,000,000. In the past two years, since starting this routine, only four times have we had counts under 3,000,000, and in each case the count has recovered within three weeks to premit resumption of treatment. All patients whose red counts run under 4,000,000 are given either inorganic iron or liver treatment. Before two years ago, when there was no rest-period every third week, and injections were given continuously, over 80 per cent of the patients needed liver or iron therapy. At present, with the rest period, it is necessary to start iron or liver therapy on less than 20 per cent of the patients who are added to the group.

A routine urinalysis is done every three weeks, but we have not as yet demonstrated any harmful effect of promin on the kidneys. We have discontinued the drug in 3.38 per cent of our patients who had a pre-existing renal insufficiency which failed to improve after moderate amounts of promin. In general, the patients receiving promin show less albuminuria, cylindruria, and hematuria than do our patients who do not receive any type of sulfone therapy.

The manifestations of sensitivity in the skin are generally mild, only 1.13 per cent of our patients having been dropped from the group because of them. In most cases the skin shows a mild eczematoid reaction which itches. In such cases the patient may be de-sensitized with small doses, starting with 0.1 Gram intravenously and increasing to 5.0 Grams after about two months. Or, a standard dose of 2.5 Grams mixed in the same syringe with 1 Gram calcium gluconate may be given daily, later increased to 5 Grams promin with 1 Gram calcium gluconate. After several months the calcium can usually be omitted.

Promin has been discontinued in 3.95 per cent of the patients reported because of the discomfort involved in daily intravenous injections. These patients requested treatment with similar sul-

fones which can be given by mouth. The most important such drug is diasone, which has been found to have an effect similar to that of promin (3,4). In addition to diasone, a small number of patients have been given a related compound, promizole, which has been studied for nearly a year, with encouraging results.

The present report, however, is based on the work with promin itself, as promin has been given to a much larger group for a much longer period of time. As a result, the information available regarding the clinical use of promin is more complete at present than it is regarding any other sulfone.

Clinical Findings: Promin has been used at the National Leprosarium for nearly five years. While the group increases in size gradually, the largest number of our 137 patients have been treated about three years, and very few for more than four years.

It has been reported and photographs have been used to demonstrate that lepromatous lesions of the skin improve. There has been no change in the observation of this phenomenon which has been continuing since the last report (2).

Mucosal lesions of leprosy are usually ulcers, nodules, and infiltrated plaques. Five years ago, before sulfone therapy had been started, the number of local treatments given in the Dental Clinic for oral lesions of leprosy averaged 3,000 per year. Since mucosal lesions respond more quickly to treatment than do cutaneous lesions, in the last fiscal year the Dental Clinic gave only 182 local treatments. While other sulfones used at the Leprosarium as well as improved local treatments have contributed to the decrease from 3,000 to 182 treatments per year, the largest single factor in the improvement of oral lesions has been the intravenous use of promin.

Neural lesions are also helped by promin treatment, but we have not observed as many cases of such improvement as we have of cutaneous and mucosal lesions because the treatment has been given largely to the lepromatous cases. However, motor function has returned in a patient who had a complete paralysis of the seventh cranial nerve; sensory function has improved in a large number of patients, frequently made painfully evident by increase in the sensation of the skin over the veins which are used daily. Trophic function appears to benefit from promin treatment in that the rate of recurrence of trophic ulcers which heal under promin treatment is extremely low (whereas ulcers that heal under treatment which is directed at the secondary infections, i.e., treatment with sulfadiazine, sulfathiazole, tyrothricin or penicillin, usually recur soon after the treatment is stopped).

The relatively permanent healing of chronic leprous ulcerations is one of the most gratifying results of the promin treatment. These ulcers of long duration are very debilitating to the patient's general health and their healing contributes tremendously to the welfare of the group. The reduction in number and severity of leprous ulcers since the inauguration of sulfone treatment at the National Leprosarium is graphically illustrated in the reduced cost of gauze, adhesive plaster, and bandages used in the ulcer clinics. The reduction in cost of such supplies for the last fiscal year was $7,419.20 as compared to 1940 (before any sulfones were started). The cost of the promin given during that period was $6,986.00.

Ophthalmic complications of leprosy have always been distressing. At present 9.5 per cent of the patients at the Leprosarium are blind. Most of these patients are blind because of a diffuse keratitis which follows multiple attacks of iridocyclitis. It has been found that such attacks occur with greatly reduced frequency if at all after promin has been given, so that promin is helping to conserve the eyes of our patients. In some cases, there has even been a reduction in density of the scars during promin treatment, with resultant improvement in visual acuity. The action of promin in eye complications of leprosy differs from that of penicillin, in that promin helps to prevent future attacks of iridiocyclitis, while it usually has little or no effect on acute inflammations while they are in progress. Conversely, in our experience, penicillin reduces markedly the duration and intensity of an inflammatory process that is in progress, but does not seem to have any value prophylactically against future attacks. Therefore, at the Leprosarium penicillin is used to abort acute attacks of iridocyclitis as a complication of leprosy, and promin to reduce or prevent future attacks.

Promin is helpful in the treatment of leprous laryngitis, as the nodules of the larynx decrease in size under treatment. At the present time, there has been no tracheotomy performed at the Leprosarium for over three years and only two patients are wearing tracheotomy tubes, both of which were inserted before sulfone treatment was started.

Laboratory Confirmation of Clinical Improvement: It is gratifying to report bacteriological confirmation of the clinical improvement which has been apparent for several years. At present, seven of our 137 patients have already passed the Parole Board and have been classified as arrested cases which are no longer a menace to the public health. While this is only 5.1 per cent, there are an additional 8.7 per cent who have had six or more consecutive monthly negative skin and nasal smears. At the

Leprosarium after a patient has had four negative skin tests a special examination of the patient is made in great detail with multiple skin scrapings made from all suspicious lesions, which are usually flattened, wrinkled, pigmented scars at the sites of former nodules. This examination is carried on in considerable detail, so that it is highly probable that the 8.7 per cent of the group which have six or more consecutive monthly negative skin tests will soon be paroled as arrested. In addition there are 34 more cases (24.8 per cent) who have had such a decrease in numbers of bacilli that the most recent skin scrapings have been negative for acid-fast bacilli. In all, at the present time, 38.6 per cent of the 137 promin treated patients are bacteriologically negative. Not only are more than a third of our group negative, but in the remaining patients it is generally more difficult to demonstrate acid-fast bacilli in the skin. A tabulation was made by grading all the skin smears from one to four plus on the basis of the relative quantity of bacilli in the skin, four plus being the largest number of bacilli. All the tests made each year of treatment were averaged, and then an average was made of all the patients who were treated that many years. The result, showing the decrease in quantity of bacilli as the period of time increases, is obvious (Figure 1).

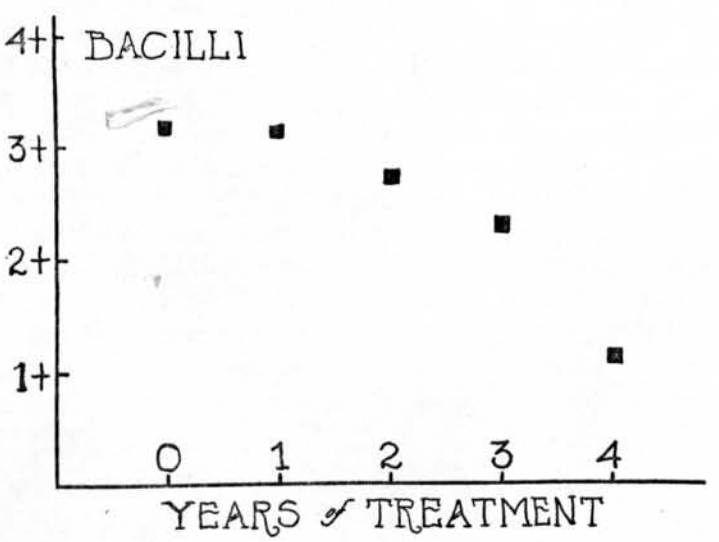

FIGURE 1

The clinical improvement has not only been confirmed by changes in the bacteriological examinations of the skin, but also it has been demonstrated histopathologically in biopsies of 32 patients who were treated for periods of time varying from 18 months to

four years. It was found that under promin treatment, the improvement in leprosy is not accompanied by characteristic cellular changes. Those which do occur are predominantly atrophic in character, with extremely slow and gradual lessening of numbers of organisms in the lesions to the point of final disappearance in 10 of the 32 cases examined. These changes do not differ materially from similar changes occurring in spontaneous remissions without treatment of any sort, or during interim periods of inactivity or regression between phases of acute activity (5,6,7,8).

The important finding is that promin appears to eliminate bacillary infection of the blood vessels and blood stream, thereby preventing the formation of new lesions. The atrophy of focal lesions is also more apparent in areas with a more generous blood supply. The results indicate strongly that the best results may be expected in those cases in which treatment is begun in a comparatively early stage of the disease.

Discussion: Two years after starting the experimental treatment with promin, it was possible to report that there was a clinical improvement in patients suffering from leprosy when treated with intravenous promin (1). Four years after starting the study of promin it was possible to report that promin was the best treatment of leprosy ever used at the National Leprosarium and that the action of promin appeared to be a chemotherapeutic effect on the etiological agent of leprosy, which could not be duplicated merely by controlling all secondary infection, as by penicillin, for example (2,9,10). Now it is possible to report that the use of promin in the treatment of leprosy results in improvement in all major, chronic manifestations of the disease and that such clinical improvement is accompanied by improvement in bacteriological and histopathological studies. It remains to be seen which drugs, chemically related to promin, will produce results more quickly and efficiently, and what percentage of the patients treated with promin will ultimately be arrested and paroled from the Leprosarium as no longer menaces to the public health.

Conclusion: The effect of 268,836 Grams of promin given intravenously to a total of 177 patients with leprosy, of whom 137 were able to continue the treatment for a period of 1-5 years has been observed. It appears from this study that promin has a chemotherapeutic effect on leprosy which is sufficiently effective that patients receiving the drug are beginning to be paroled from the Leprosarium as arrested and no longer menaces to the public health.

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