LOCAL TREATMENT OF LEPROUS ULCERS WITH CRUDE PREPARATIONS OF STREPTOMYCIN*

by

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INTRODUCTION

One of the most frequent and difficult conditions encountered in the management of leprosy is the occurrence of associated cutaneous ulcers. Many of them are resistant to all known methods of treatment, and many contribute greatly toward undermining the patients' general health. Their painful and crippling effects immobilize many individuals, and the disease as a whole becomes worse. The repulsiveness of the ulcers to the patient, nurse, and physician alike, makes any treatment which keeps them clean and free of odor, and which demonstrates some signs of stimulation toward healing, worthy of use in the management thereof.

Faget and Pogge (1) are of the opinion that "sulfanilamide, sulfathiazole, sulfadiazine, and penicillin are potent in clearing up secondary pyogenic infections and in healing chronic ulcerations," but find "less tendency for ulcers to recur when healed under the influence of promin than when healed under the influence of these other chemotherapeutic agents." This they explain as probably due to a chemotherapeutic effect of promin on leprosy. They are also of the opinion that by clearing up secondary infection promin has an indirect effect in the healing of ulcers in leprosy.

During the past five years there has been a marked steady decrease in the number of cutaneous ulcers seen in the patients being treated in the National Leprosarium at Carville, Louisiana. The cost of supplying bandages and dressings for treating ulcers has decreased to such an extent that it has more than balanced the cost of providing the new sulfone drugs now employed as routine treatment of leprosy at this hospital. This decrease in number of ulcers encountered is undoubtedly due to the use of promin, diasone, and promizole systemically, and sulfathiazole, sulfadiazine, and penicillin both locally and systemically.

Although great progress has been made, ulcers resistant to

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treatment are still being encountered. These are generally of the trophic or perforating type, or those found on a lepromatous base in an individual having some nutritional disturbance. The leprous ulcer in which there is little or no trophic element usually responds readily to promin and the sulfonamide drugs.

Streptomycin has been reported (2, 3) to be bacteriostatic and bactericidal *in vitro* against *M. tuberculosis,* an acid-fast organism morphologically similar to *M. leprae.* This new antibiotic, produced in cultures of the fungus *Streptomyces griseus,* the natural habitat of which is the soil, has been reported (4) as effective also *in vitro* against a variety of gram-negative organisms including the common offenders in infected cutaneous ulcers.

A culture of *Streptomyces griseus* was obtained through the courtesy of Dr. S. A. Waksman and from this, simple broth cultures were prepared. The crude filtrate of the cultures has been used since January 1, 1946 in the treatment of leprous and trophic ulcers as described below.

MATERIALS AND METHODS

Cultures of *Streptomyces griseus* are planted in 1000 cc. precipitation bottles containing 200 cc. of autoclaved broth of the following formula:

Beef extract	5 Gms.
Sodium chloride	5 Gms.
Proteose peptone	10 Gms.
Dextrose	10 Gms.
Water q.s.	1000 cc.

The pH of this medium is adjusted to 6.8 to 7.0. The cultures are incubated for seven days at room temperature, the precipitation bottles being placed in a horizontal position allowing only a shallow depth of media. After incubation, cultures are filtered through ordinary filter paper and the filtrate is used therapeutically without further treatment or sterilization, because heating destroys much of the streptomycin. It is preserved in liter bottles at 4° C. If not used within ten days the filtrate is discarded.

The average pH of the crude filtrate is 8.5. Assays of the amount of streptomycin in the filtrate have shown yields of 28 to 40 micrograms per cc.

Patients who are to be treated with the streptomycin broth are hospitalized and put on bed rest with commode privileges only. Layers of gauze which has been thoroughly soaked in the full strength filtrate are applied to the ulcer or ulcers under treatment. Several layers of bandages are applied to keep the dressing in place.

A rubber apron or moisture-proof piece of paper is wrapped about the foot, hand, limb, or area treated, to prevent excessive drying. The dressing is soaked every twelve hours with full strength crude streptomycin broth and left in place for one week after which a new dressing is applied. Treatment is continued in this manner until the ulcer is healed, unless the odor becomes offensive or the patient complains of discomfort or symptoms which would indicate excessive absorption of, or irritation by, the streptomycin broth.

In case of offensive odor the dressing is changed twice or thrice weekly. It is usually necessary to make a more frequent change of the dressing only during the first week or two of treatment. After that the ulcer becomes clean and the dressing usually remains free from any repulsive odor.

Itching of the extremity treated has been a complaint in a few cases. The dressing is removed in such cases and the area of treatment inspected. An area of erythema with vesiculation is usually found indicating irritation or local sensitivity to the drug. It is sufficient to dilute the filtrate with boric acid solution 1 to 5 and apply this instead of the full strength filtrate. If symptoms continue the dressing is removed and the affected part exposed to the air for a day or two, or the wet dressing may be changed to straight boric acid for one week. The erythema and vesiculation disappear and treatment can be resumed.

Some patients complain of a sour taste in the mouth after the first day or two of treatment. This is apparently due to absorption. A tolerance for this is usually built up but a patient, now and then, will later develop nausea and vomiting. Reduction of the strength of the filtrate by dilution with boric acid solution has been sufficient to eliminate these symptoms except in one case in which the treatment had to be discontinued because of severe anorexia, nausea and vomiting, even on the more dilute solution.

RESULTS

Thirty-six patients have been treated thus far. Toxic manifestations have been almost non-existent. Treatment had to be discontinued in only one case on this account. Treatment of one patient with extensive ulcers on both hands was discontinued after one week's treatment because of personal objection by the patient to the bandages. This leaves thirty-four cases to be considered in the results obtained.

SELECTED CASE REPORTS

CASE 1. No. 859. White female, aged 59, with far advanced mixed leprosy, predominately neural, of seventeen years duration, and perforat-

ing plantar ulcers of seven years duration. These healed for a short time in 1944, but a painful callus remained, and they soon broke down again. While on systemic diasone therapy, treatment with streptomycin broth was begun of three perforating ulcers of the sole of the left foot. The largest ulcer opposite the fifth metatarsal bone was 1.6 by 1.0 cm. in size. This healed on the thirty-sixth day of treatment, the other two on the twenty-second day, without recurrence.

CASE 2. No. 949. White male, aged 46, with far advanced mixed leprosy, predominately neural, of twenty-two years duration, and an indolent ulcer of the lateral aspect of the left foot of ten years duration, which had resisted all types of treatment. This measured 4.0 by 3.5 cm. in diameter, by 4.0 cm. deep, at the time of institution of treatment with streptomycin broth. On the forty-eighth day of treatment the ulcer measured 1.5 by 1.9 cm. and was 60 per cent healed. The patient was always unable to walk, and rest had been no greater than before.

CASE 3. No. 1401. White male, aged 23, with moderately advanced mixed leprosy of eight years' duration, and a perforating plantar ulcer of four years' duration. This healed for about two months a year ago, but broke down again and resisted all forms of routine treatment. At beginning of treatment with streptomycin broth the ulcer measured 1.5 by 1.8 cm. in diameter and was 1.0 cm. deep. Complete healing with softening and peeling of a hard callus was obtained on the thirty-fifth day of treatment, without recurrence.

CASE 4. No. 1563. White male, aged 40, with moderately advanced lepromatous type of the disease, and large infected painful ulcers of both legs of three years' duration. Numerous and various treatments of ulcers had never produced full healing. While on systemic promin therapy, local treatment of the ulcers with streptomycin broth produced complete healing in ninety-seven days. On unrestricted activity these recurred, and treatment was begun again. One large ulcer on the leg measured 5.0 by 7.0 cm. In three months this and other lesions were 90 per cent healed.

CASE 5. No. 1750. White male, aged 58, with far advanced mixed leprosy of twenty-two years duration, undernourished and generally in poor condition, with severe extensive ulcers of both lower extremities below the knees. Systemic promin therapy and local application of streptomycin broth were begun at the same time. He has shown steady improvement, with the ulcers 90 per cent healed in seven months of treatment.

CASE 6. No. 1775. White female, aged 60, with moderately advanced mixed leprosy of eight years duration, and an ulcer of the heel for two months. Treatment of the ulcer with streptomycin broth and systemic treatment with diasone were begun simultaneously. The ulcer was 6.0 cm. in diameter, the bed showing much granulation tissue. Complete healing was obtained on the sixtieth day of treatment, without recurrence.

SUMMARY OF CASE REPORTS

The patients treated with streptomycin broth may be divided into three groups on the basis of the type of ulcer involved:

Group I. Pure trophic perforating ulcers of the sole of the foot.

Group II. Ulcers with some lepromatous element in addition to a trophic or nutritional factor.

Group III. Leprous ulcers without apparent nutritional disturbance.

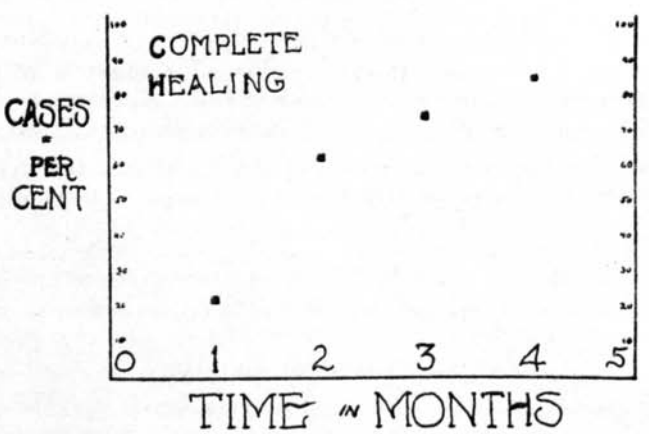
The majority of cases treated with streptomycin broth had previously been treated varying lengths of time with various agents including sulfonamide drugs and penicillin locally and systemically. All, at the time the treatment with streptomycin broth was commenced, were either stationary or regressing.

TABLE I: *Results of Treatment*

GROUP	CASES	Successful Results	
		Cases	Percent
I Trophic	19	18	94
II Mixed	14	11	79
III Lepromatous	1	1	100
TOTAL	34	30	88

Table I shows the type of ulcer treated, number of patients in each group, and number and per cent of successful cases. Figure 1 shows the length of time required to secure complete healing.

FIGURE I *Time required for complete healing*



The type of ulcer most resistant to treatment was the large

sloughing variety which is usually found about the lower third of the leg including the ankle and dorsum of the foot. The majority of the ulcers in Group II were of this variety. This type of ulcer was completely healed in only 45 per cent of cases in less than two months, and satisfactory results were obtained in only 11 of the 14 cases treated (80 per cent). The most satisfactory results were obtained in the perforating ulcers of the sole of the foot (Group I) which are commonly considered true trophic ulcers. These ulcers are usually very resistant to treatment. Only one of the 19 cases failed to heal satisfactorily, and this was a case in which there was bone involvement. Of the remaining 18 cases, 15 or 80 per cent healed in less than two months. The single case of a true lepromatous ulcer (Group III) healed very rapidly. Before treatment, bacteriologic examination showed it to be teeming with acid-fast organisms. Complete healing was secured in about ten days. The patient who required over four months for healing was a far advanced mixed case in which 90 per cent of the surface of the legs and feet presented ulcers. One blind patient who has been unable to get around except in a wheel chair has had a deep perforating ulcer for nine years on the lateral aspect of a flail left foot. After six weeks of treatment during which there was little change in the activity of the patient, the ulcer was 60 per cent healed.

Taking all the groups of treated ulcers together, approximately one-fourth (23 per cent) of the cases healed satisfactorily in less than one month. Another month's treatment found approximately three-fourths (70 per cent) of the cases satisfactorily healed.

DISCUSSION

The crude filtrate of the broth has been shown to contain most of the elements of the original ingredients. The glucose is not utilized by the growth of the mold. Thus some of the beneficial effect of the broth may be due to the highly nutritive protein derivatives and carbohydrates present. It is also probable that the occasional irritation results from substances in the original ingredients, such as the peptone, rather than the streptomycin.

Streptomycin in solution is a moderately stable substance, unlike penicillin in this respect. Although less stable in solution than in dry form, solutions appear to maintain their strength for some time in the ice box, and discarding of the solution after ten days in the ice box is done partly because of possibility of contamination by bacteria and fungi capable of growing at low temperatures. Most bacteria appear not to destroy streptomycin (5), and it is

probable that the amount of the drug in the dressing is well maintained over the twelve hour period between soakings.

The amount of streptomycin in the broth (averaging 35 micrograms per cc.) is sufficient to prevent gross contamination in the dressing for a significant period of time. When the pure original broth medium was used in the dressings as a control, it was found that the dressings became rapidly putrid. The concentration of the streptomycin in the broth is roughly the same as produced in the circulating blood from intramuscular injection of a therapeutic dose of the pure drug. Obviously its effect can be only local, and although absorbable from open ulcers, the drug could not be absorbed in quantity sufficient to produce a blood level of therapeutic value.

Up to the present time, it has not been possible to obtain the pure drug for direct application to ulcers. While it is hoped that this will eventually become available, it should be emphasized that this crude filtrate can be prepared easily and cheaply with a minimum of laboratory equipment. It is also hoped that further experimentation with other basic media (6) will increase the yield of streptomycin and decrease the local irritation.

Although the results obtained can not be termed dramatic they are most encouraging when it is kept in mind that the majority of these cases were resistant to all other methods of treatment used.

Cases presenting infected painful cutaneous ulcers with fever and beginning lymphagitis were usually free of pain and fever after the first twenty-four hours of treatment. One patient with a rather painful ulcer of six years duration stated after the first week of treatment that she was free of pain for the first time in six years.

After the first week of treatment the ulcer bed is found clean with beginning granulations at the edges. Islands of epithelium sometimes form over the ulcer base in the large superficial sloughing type of ulcer. Excessive formation of granulation tissue and bleeding are apt to occur in some cases. This occurrence is easily controlled by the application of silver nitrate in strengths sufficient to cauterize the granulating area mildly.

Around the perforating ulcers of the sole of the foot there is usually a thick callus. In some of our cases this callus has been as much as 1 cm. thick. After two or three weeks of treatment the callus softens and peels off leaving a smooth layer of skin with the ulcer bed almost completely filled with new epithelium. In this type of ulcer recurrences are kept to a minimum by the use of sponge rubber pads of a thickness of one-fourth to one-half of an

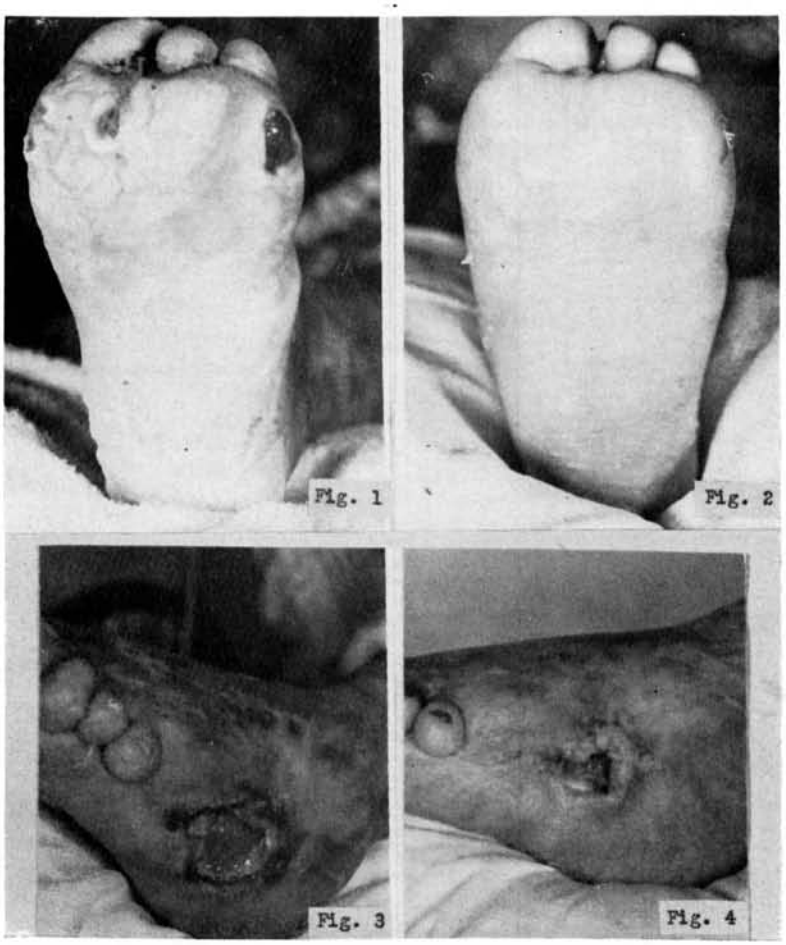


Fig. 1. Case 1 before treatment.
Fig. 2. Case 1 after six weeks' treatment.
Fig. 3. Case 2 before treatment.
Fig. 4. Case 2 after seven weeks' treatment.

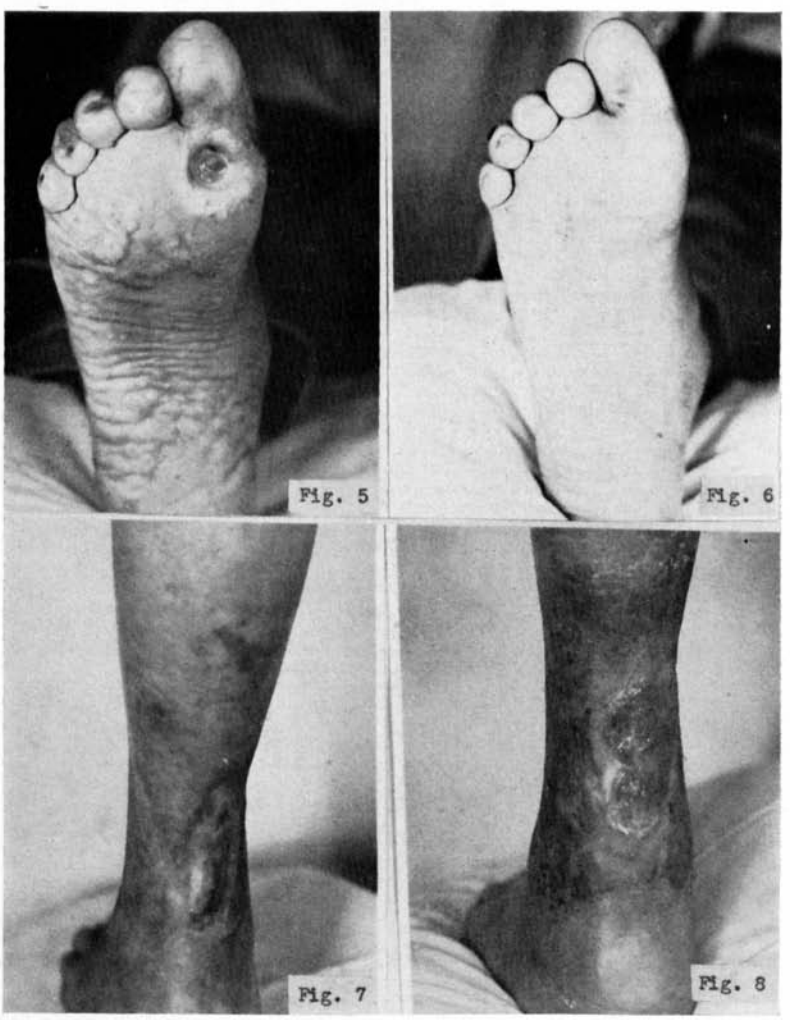


Fig. 5. Case 3 before treatment.
Fig. 6. Case 3 after six weeks' treatment.
Fig. 7. Case 4 before treatment.
Fig. 8. Case 4 after three months' treatment.

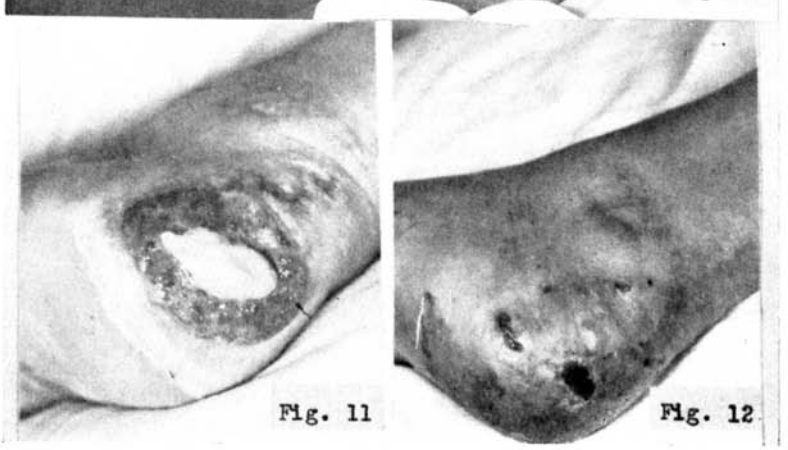


Fig. 9. Case 5 before treatment.
Fig. 10. Case 5 after five months' treatment.
Fig. 11. Case 6 before treatment.
Fig. 12. Case 6 after eight weeks' treatment.

inch in the shoes, to relieve the pressure on the sole of the foot in standing and walking.

Bed rest is undoubtedly a factor to consider in the healing of ulcers under this regime. However, it cannot very well be the sole factor responsible for the favorable results. None of the patients treated engaged in any heavy physical activity prior to treatment with the streptomycin broth.

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