USE OF STREPTOMYCIN IN THE TREATMENT OF LEPROSY*

A Preliminary Report

by

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Streptomycin was first isolated in 1944 by Selman A. Waksman and his co-workers at the New Jersey Agricultural Experimental Station, Rutgers University, from cultures of certain strains of the actinomycete, the *Streptomyces griseus*. From the original and subsequent reports (1, 2) of this group of investigators it appeared likely that streptomycin exerted antibacterial activity against a variety of gram-negative and some gram-positive pathogens including *Mycobacterium tuberculosis*. When the studies of Feldman and Hinshaw (3) demonstrated that streptomycin exerted suppressive effect on experimental tuberculosis in the guinea pig, the senior author became definitely interested in its possible therapeutic value in clinical leprosy. Through correspondence with Selman A. Waksman and through the courtesy of Dr. J. M. Carlisle of Merck & Company, Incorporated, he received 50 million units of streptomycin in the summer of 1945 for experimental purposes in leprosy. This was sufficient for the treatment of only one patient. Treatment was started on this patient on July 28 and ended on September 17, 1945. After an observation of several months following treatment it was felt that the results, although not definite, were encouraging. This case greatly stimulated interest in further streptomycin therapy of leprosy and it was determined that it should be tried on a more extensive scale as soon as an adequate supply became available for this purpose.

The later report of Hinshaw and Feldman (4) that streptomycin might prove useful in some types of clinical tuberculosis increased the importance of its further assay in leprosy. The report of the remarkable healing of laryngeal tuberculosis in a case treated with streptomycin (5) reported by the above authors was another feature of the drug which particularly appealed to the medical staff of the National Leprosarium.

It was not until June 1946 that an adequate amount of strep-

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tomycin was made available as part of the supply allotted to the U. S. Public Health Service. It was decided to place 10 selected leprosy patients on a four months' course of intensive treatment with streptomycin. At the end of that period since the results were not conclusive it was decided to prolong the treatment with reduced dosage for another four months which brings the experimental study to the present date.

TECHNIC OF ADMINISTRATION

The streptomycin used in this study was obtained from three different pharmaceutical firms. It was administered in 10 selected cases of lepromatous leprosy intramuscularly in doses of ¼ gram (250,000 "s" units) every three hours for a total of 2 grams (2,000,000 "s" units) in twenty-four hours. Each gram lot was dissolved in 6 cubic centimeters of physiologic saline solution, making the volume of each injection 1.5 cubic centimeters. This treatment was continued without interruption, except in 2 cases, for a period of four months. Thereafter the dosage was diminished to ½ gram every twelve hours or a total of 1 gram (1,000,000 "s" units or micrograms) in twenty-four hours. The latter dose is still being administered at present and will be continued for a few more weeks.

TOXIC MANIFESTATIONS

Early reports on streptomycin even when the less pure preparations were being utilized describes it as a drug of low toxicity. It appears from our experience, however, that this is true only when comparatively small doses are given over short periods of time. With higher dosage and more prolonged treatment the incidence of toxic reactions increases considerably. When high dosages are given over a period of months, serious toxic effects are apt to occur and the less serious and more common ones may become exceedingly unpleasant to the patient (see Table I).

The most serious complications encountered were tinnitus and impaired hearing, and an exfoliative dermatitis. The more common and rather severe toxic manifestations were vertigo, fever, and skin eruptions. Less serious conditions were eosinophilia in all cases, fall in blood pressure in 9 cases, headache in 7 cases, malaise in 8 cases, flushing of skin in 5 cases, nausea and vomiting in 4 cases, transient diplopia in 1 case, diarrhea in 2 cases, and appearance of albumin and casts in urine in 7 cases. All of these latter mentioned effects have been attributed to impurities contained in earlier preparations of streptomycin but were here encountered with supposedly highly refined products.

TABLE I. *Summary of toxic effects encountered*

Toxic effect	Number of Patients
Vertigo	10
Eosinophilia (with leucocytosis)	10
Soreness of site of injection	10
Decrease in erythrocytes (500,000) and hemoglobin (10%)	9
Loss of weight	9
Fall in blood pressure	9
Fever and malaise (with arthralgia —3)	8
Headache	7
Casts and red blood cells in urine (renal impairment—1)	7
Flushing of skin	5
Anorexia, severe	4
Nausea and vomiting	4
Skin eruptions	4
Pruritis without eruption	3
Diarrhea and abdominal cramps	2
Tinnitus and impaired hearing	1

Vertigo occurring in all of the patients treated began during the first week in 3 patients, the second week in 2, the third week in 3, and during the fourth and fifth weeks in the remaining two patients. Vertigo was classified as severe in 4, moderate in 3, and mild in 3. Severe cases were those in which the patient was so dizzy when up that he preferred to stay in bed. Nausea and vomiting were frequent in such cases. Moderate cases were those where patients were so wobbly on their feet that they generally walked close to the walls for support and spent most of their time sitting in their rooms or on the porch of the hospital. Mild cases were usually ambulatory but could not walk a straight line and swayed considerably in the Rhomberg test. Vertigo was still present in all patients but mild in character at the end of eight months' treatment.

Eosinophilia occurring in all of the patients treated started within the first two weeks of treatment and progressively increased to a peak in the twelfth week to 3400 cells per cu. ml. of blood. Slowly declining during the next four weeks to 1200 cells, it became stationary until two weeks after reducing dose by one-half; then it declined again. Eosinophilia was still present in all patients at the end of the above mentioned treatment period. Usually 10 to 20 per cent was the differential eosinophile count. It varied from a low of 4 to 5 per cent to individual heights of 42, 43, 47, 54, and 65 per cent.

Low grade progressive anemia developed in 9 patients in the early weeks of treatment but responded well to administration of

iron and liver extract. The loss of erythrocytes amounted to from 500,000 to 1,000,000 per cu. ml. in 7 patients, and from 1,000,000 to 2,000,000 in 2 patients.

Loss of weight averaging 9 lbs. due to anorexia, malaise, nausea and vomiting, and loss of sleep occurred in 9 patients. After diminishing the dosage, 5 patients regained weight and showed an average increase of 6 pounds over their initial weights. Four are still underweight by an average of 7 pounds.

There was a fall in blood pressure of from 10 to 40 mm. of mercury in both diastolic and systolic phases in 9 patients. This hypotension seemed to vary directly with the severity of the vertigo in most cases.

Fever and malaise were present in 8 patients. Onset was on the first to the eighth day of therapy in most cases and the duration a week to a month or longer. Low grade fevers of 37.4° to 38° C. was the usual occurrence, but occasionally it rose to 39° C. or slightly higher. Fever accompanied all cases of skin eruption and arthralgias. In 5 patients it was associated with erythema nodosum, neuritis, or lymphadenopathy; but in 3 patients there was nothing to account for the fever except streptomycin.

Headache occurred in 7 patients. In 3 it was transient but in 4 it seemed to be a part of a histamine-like reaction, occurring with flushing of the the skin, fall in blood pressure, and nausea and vomiting.

Renal irritation occurred in 7 patients who showed the appearance of red blood cells and casts in the urine during the early weeks of treatment. In one patient there also developed albuminuria and impaired renal function with increase of the N. P. N. from 28 to 53 mg. per cent. During the last few weeks urinalyses have shown negative findings in this patient.

Skin eruptions occurred in 4 patients and pruritis without skin eruptions in 3 others. The skin eruptions developed on the seventh and eighth days in 3 patients. In the other, a white male aged 58, it first appeared on the second day followed by a recurrence on the thirty-ninth day. This second attack developed into a severe generalized exfoliative dermatitis with an eosinophile count of 65 per cent and a leucocytosis. This dermatitis subsided in a week after the discontinuance of streptomycin. Small gradually increasing doses were then prescribed in order to desensitize him. Unfortunately through error a larger dose than intended was injected and the dermatitis promptly recurred. It abated again upon discontinuing streptomycin and the patient became desensitized by

starting with a 1/10 gram dose which was gradually increased. At present he is on full (½ gram) doses twice daily like the other patients.

Diarrhea and abdominal cramps occurred in 2 patients. In one the symptoms were mild and subsided spontaneously. In the other they were more severe but relieved on decreasing the dose of streptomycin. They promptly recurred when dosage was again increased. Smaller dosages permanently relieved the condition.

Tinnitus and impaired hearing occurred in one patient. This patient, a white female, aged 31 years, was known to have had impaired renal function prior to treatment and was under careful observation. At the end of the first week of therapy this patient developed flushing of the face and a generalized maculo-papular skin eruption. Streptomycin was promptly discontinued. After symptoms subsided treatment was resumed with one-fourth of the previous dose. Subsequently, upon gradually increasing the dosage, a severe vertigo occurred during the third week. Tinnitus and impaired hearing then occurred when the streptomycin blood level was found to be 41 "s" units per cc. of blood. The dosage was again reduced to one-fourth and tinnitus subsided but impaired hearing persisted. An audiometer reading taken in the fifth month of treatment showed loss of useful hearing in the left ear and reduction of hearing to 50 per cent in the right ear. Streptomycin therapy was permanently discontinued and five weeks later a repeat of the audiogram showed only slight improvement of auditory function. Since then hearing appears to be returning gradually and it is hoped that impairment of hearing will not be permanent.

Soreness and inflammation at the site of injection was a minor reaction. However, with one preparation all patients complained bitterly of pain following injection of the drug and subsequently developed inflammatory masses at the site of injection which were exceedingly painful to palpation.

EFFECTS ON LEPROSY

The therapeutic effects of streptomycin in leprosy are not as yet conclusively demonstrated but encouraging changes seem to have occurred in some cases. Nasal obstruction and epistaxis have been checked in a few cases. Healing of a leprous ulcer of the soft palate occurred rather rapidly in one patient. Bacteriologically there have not been any reversals so far from positive to negative skin or nasal smears. The reports of the monthly bacteriologic skin and nasal smears seem to indicate however a decrease in the numbers of acid-fast organisms in 8 cases. There has been an improve-

ment in the sedimentation rate of 3 patients. In the blood serology 7 of the 9 patients with presumably false positive or doubtful serologic tests for syphilis showed improvement in a lessened degree of positivity or a change from doubtful to negative.

There appear to be some photographic changes on the improvement side in some of the nodular and macular lesions of the patients under treatment.

Among the 10 patients treated there were 7 men and 3 women; 9 were white and 1 colored. They were all lepromatous cases of moderate to far advanced stages. Five patients were treated with streptomycin alone; of this number 4 had had no previous treatment, while one had had a previous course of streptomycin.

Four patients were treated with streptomycin and promin. They had all been on promin for several months to two and one-half years prior to starting streptomycin and each had shown slight improvement although new nodules had developed in one of them. Since the improvement did not seem to be as rapid or as extensive in them as is usually the case with promin therapy, streptomycin was added in the expectation that it would hasten the improvement.

One patient who had had no previous treatment was started on diasone in addition to streptomycin to note if the progress of her improvement would not be more rapid than that of those on streptomycin alone. She did make good improvement, but it is difficult to say that this improvement was more rapid than that noted in the others.

RESPONSE TO STREPTOMYCIN AND STREPTOMYCIN-SULFONE THERAPY

Degree of response	Streptomycin		Streptomycin-sulfone		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
Definitely improved	1	20.0	1	20.0	2	20.0
Slightly improved	2	40.0	3	60.0	5	50.0
Stationary	1	20.0	1	20.0	2	20.0
Slightly worse	1	20.0	0	00.0	1	10.0
Total	5	100.0	5	100.0	10	100.0

The above table sets forth the degree of response to treatment

experienced to date in the streptomycin and streptomycin-sulfone groups of patients. By clinical, laboratory, and photographic study, 20 per cent registered definite improvement, and 50 per cent showed slight improvement. Two, or 20 per cent, remained stationary and one, or 10 per cent, became slightly worse. The degree of response to treatment seemed slightly better with streptomycin-sulfones than with streptomycin alone but the numbers treated are too small to give statistical evidence of this.

LOCAL APPLICATION OF STREPTOMYCIN

Streptomycin has also been used locally in the treatment of leprous ulcerations with good results (6). This streptomycin was prepared locally from filtrates of cultures of *Streptomyces griseus* grown in the station laboratory. This filtrate at first was used as wet dressings. In a few instances there occurred a local irritation of the surrounding skin. In such instances the filtrate was diluted with boric acid solution. This resulted in subsidence of the local toxic reaction.

More recently the streptomycin filtrate has been incorporated into an ointment base. This is a more soothing application and seems to produce more rapid disinfection and healing of ulcers.

Some very stubborn ulcers, which had previously resisted other types of treatments, such as the sulfa drugs, penicillin, and tyrothricin, seemed to respond slowly but surely to the streptomycin applications.

Although the results in ulcer healing are encouraging, it must be stated that the production of streptomycin in the local laboratory is a too laborious and time-consuming procedure for general adoption. For this reason it is felt that it would be more economical as well as more efficient to use the purified streptomycin powder of pharmaceutical firms in the preparation of an ointment for local application to ulcers.

DISCUSSION

Streptomycin produces encouraging results in the treatment of leprosy.

In large and continuous dosage its toxic manifestations seem to be too severe in comparison with results obtained.

Deafness in one patient which has improved only slightly to date may be too dear a price to pay for the benefits obtained.

It is the impression of the writers that unless streptomycin can be further purified to render it less toxic or the effective therapeutic dose can be reduced, or a different method of administration developed, such as streptomycin suspension in oil and wax, strep-

tomycin will probably not become the treatment of choice for leprosy.

For comparable results the sulfones have thus far been found to be less toxic and therefore more feasible in the treatment of leprosy.

The improvement observed is not appreciably more rapid than that obtainable with the sulfones. Whether this improvement will be progressive with continued treatment, as is the case with the sulfones, is problematic.

Perhaps smaller doses of streptomycin will be found to enhance the therapeutic action of the sulfones and such a combination will prove to be the best future treatment of leprosy.

At the recommended dosage of 2 grams daily (2,000,000 "s" units) given for prolonged periods, streptomycin seems too toxic and its mode of administration too disturbing to the patient to be of practical value.

It is the writers' opinion that further investigation of streptomycin therapy in leprosy must continue before conclusive evidence of its clinical effect can be determined.

Streptomycin seems to be an effective agent in the local treatment of chronic leprous ulcerations. Its study in this field should be continued by using it as wet dressings and in ointment bases to observe the best method of topical application as well as the optical concentration for curative effect.

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