INTERNATIONAL JOURNAL OF LEPROSY

VOLUME 18, NUMBER 4 OCTOBER-DECEMBER, 1950

THIOSEMICARBAZONE (TB-1) IN THE TREATMENT OF LEPROSY
PRELIMINARY COMMUNICATION

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The favorable results obtained in Germany with the thiosemicarbazone called TB-1—or "conteben"—in the treatment of tuberculosis, based on the experimental work of Domagk (1), suggested the possibility that this drug might be therapeutically active in leprosy. With respect to that disease there has as yet been only one report, by Hohenner (2), of the treatment of a single case.

During December 1949, Professor Domagk was in Venezuela and visited the Cabo Blanco leprosy hospital with us. After a discussion regarding the possible therapeutic action of thiosemicarbazone in leprosy, the possibility that tolerance of the drug might be better in leprosy than in tuberculosis, and the possibility that in leprosy it might prove superior in its effects to the already known sulfa drugs, it was agreed that an experimental trial of it should be made at Cabo Blanco, the drug to be supplied without charge by the Bayer Laboratories of Leverkusen, Germany.

The writers thereupon established a program based on the norms laid down by the Fifth International Leprosy Congress, the known pharmacological data of this new drug, and the experience in its use in the treatment of tuberculosis, as well as the rules which since 1945 have been followed in Cabo Blanco in the treatment of leprosy with sulfa drugs generally.

MATERIALS AND METHODS

Acquisition of the drug.—During the first week of March we received from the Bayer Laboratories an amount of drug equivalent to 9,000 tablets of 0.05 gm. each. This amount, we calculated, was enough to treat 40 patients for only 4 months, which was obviously an insufficient period of time to determine the value of the drug. We therefore asked our Health Department to buy the amount required to continue the experiment for one year, and that was done, thus assuring the continuity of the experiment.

Selection of cases.—For the experiment we selected 42 cases of the lepromatous type of varying degrees of severity, from those which presented merely macules to quite advanced (L3) forms. The major problem encountered was to find suitable cases which had had no previous treatment, for in Venezuela there are practically no leprosy patients in confinement who have not been treated.

The group selected has the advantage that it contains a certain number of women and children, purposely included so as to obtain data regarding their tolerance of the drug. The 43 cases comprise 37 males and 6 females; and there are 7 children.

Examinations.—All of the patients were examined clinically, and proper records made, with regard to lesions of the skin, mucous membranes, and eyes, as well as of the peripheral nerves. Bacteriological examinations of the skin and nasal mucosa were made, the Mitsuda test was applied, biopsy specimens of the skin were removed for histopathological examination, and photographs were taken. Clinical and radiological examinations of the thorax were also made.

Laboratory examinations were made of the blood (cell counts and sedimentation rates), the urine, the feces, the liver function (bromsulphothalein, Takata-Ara, and Uko tests), and blood sugar and urea nitrogen determinations were made.

Reexaminations.—It was decided that, for purposes of control, every three months the dermatological and bacteriological examinations should be repeated; that every six months the histopathological examinations should be repeated and new photographs taken; and that each year new neurological and immunological examinations should be made.

For laboratory control, it was decided that every two weeks the blood counts, sedimentation-rate determinations, and urine examinations should be repeated; that every four weeks, urea nitrogen and blood sugar examinations should be made; and that every 8 weeks tests of liver function should be performed.

Dosage.—Care was taken that the doses of the drug given should be in accord with the age and weight of the patients. With the adults, the beginning dose was set at 25 mgm., and with the children 5 mgm. For the former, the dose was increased by 25 mgm. weekly; for the latter, the original dose was maintained for the first month and then slowly increased until 25 mgm. was reached.

It was our expectation, which has been confirmed by our experience so far, that in leprosy it would be possible to reach

much higher dose levels than in tuberculosis. It appears that the majority of German workers who have been using TB-1 have concluded that the intolerance observed in tuberculosis patients is due to the liberation of toxins by the destruction of large quantities of bacilli, but in leprosy—at least lepromatous leprosy, with its anergy to the bacillary products—it is to be expected that the destruction of *Mycobacterium leprae* will not be followed by effects which could be ascribed to any such process.

Our experience has led to a modification of the original schedule of increase of doses, because of lack of intolerance of the drug. Consequently, in some of our patients the dose has been increased at the rate of 50 mgm. per week instead of 25 mgm. At present the distribution of the daily dosage schedule is as follows:

900 mgm.	(18 tablets)	1 patient
750 mgm.	(15 tablets)	2 patients
700 mgm.	(14 tablets)	3 patients
650 mgm.	(13 tablets)	6 patients
600 mgm.	(12 tablets)	4 patients
550 mgm.	(11 tablets)	5 patients
500 mgm.	(10 tablets)	1 patient
350 mgm.	(7 tablets)	6 patients
300 mgm.	(6 tablets)	2 patients
200 mgm.	(4 tablets)	2 patients
150 mgm.	(3 tablets)	3 patients
100 mgm.	(2 tablets)	6 patients
50 mgm.	(1 tablet)	2 patients

Because we have not observed any blood changes, or liver disfunction, or other indications of visceral lesions, we have increased the daily dose in 28 patients above 300 mgm. which is the dose commonly used in tuberculosis.

The total amounts of the drug taken in the six months which have elapsed since the experiment was started are as follow:

Over 1,600 tablets	(over 80 gm.)	1 patient
1000—1,100 tablets	(50—55 gm.)	5 patients
900—1,000 tablets	(45—50 gm.)	7 patients
800— 900 tablets	(40—45 gm.)	7 patients
700— 800 tablets	(35—40 gm.)	4 patients
600— 700 tablets	(30—35 gm.)	3 patients
500— 600 tablets	(25—30 gm.)	4 patients
400— 500 tablets	(20—25 gm.)	6 patients
300— 400 tablets	(15—20 gm.)	2 patients
200— 300 tablets	(10—15 gm.)	2 patients
100— 200 tablets	(5—10 gm.)	2 patients

RESULTS OBTAINED

At the time of this preliminary report, September 8, 1950, the duration of the treatment period, begun on March 7, was 6 months in 30 cases, 5 months in 4 cases, 4 months in one case, 3 months in 7 cases, 2 months in one case.

Regression of skin lesions.—Regression of erythematous macules, nodules and infiltrations (in "plaques" and diffuse), was evident after the second month. At the end of the fourth month, erythematous macules as well as nodules had disappeared in a considerable number of patients, the infiltrations had regressed appreciably, and the lesions of the mucosa were notably better. The statistics of these changes are as follows:

In five and six months:	
Very important regression of lesions	21 patients
Important regression of lesions	7 patients
Partial regression	6 patients
In three and four months:	
Very important regression of lesions	1 patient
Important regression of lesions	2 patients
Partial regression	5 patients
In two months:	
Partial regression of lesions	1 patient

These data show that all of the patients treated for more than two months had evident regression of their lesions, varying from very important to only partial.

Bacteriological changes.—Bacteriological examinations showed that in only 4 cases was there appreciable decrease in the number of bacilli. However, fragmentation of bacilli was observed in some cases.

Other observations.—The sedimentation rate decreased in an important manner in 16 of the patients treated, in keeping with their improvement. Twenty-seven of the patients (63%) have had reaction during the course of treatment. In two cases, the reactions necessitated suspension of the drug. In the rest of the patients the reactions were mild and subsided after the reduction in the dose. In one case the treatment was started during a mild lepra reaction and was continued without exacerbation of the process.

CONCLUSIONS

At the Cabo Blanco leprosarium, in Venezuela, an experiment is under way in the treatment of leprosy with a thiosemicarbazone, "TB-1." It was considered probable, because of results

already obtained in Germany in tuberculosis, and also in one leprosy patient treated for a short period of time, that this drug would be active in leprosy.

This experiment was set up with a program of the necessary control examinations during the course of the treatment, in order to observe the patients' tolerance to the drug and its therapeutic effects.

At the time of writing 42 lepromatous cases have been treated for periods of 3 to 6 months (March to September 1950). The initial results observed indicate marked therapeutic activity; during the short period of experiment to date notable clinical regression of leprous lesions has been observed.

No manifestations of intolerance have been observed with respect to blood changes or disturbance of the liver or other viscera.

This preliminary communication is published because of our conviction that much benefit may be derived from the application of this thiosemicarbazone in the treatment of leprosy.

REFERENCES

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