

## THIOSEMICARBAZONE AS AN ADDITIVE IN THE TREATMENT OF LEPROSY

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In October 1950, fifty leprosy patients were selected for treatment with thiosemicarbazone (TB-1). There was a wastage of seven cases: there were three deaths, not connected with therapy; one patient refused to continue treatment; and three absconded. The results in the remaining 43 cases, at the end of three and one-half years of treatment, are reported here.

The cases were selected out of two groups, those that had had and those that had not had sulfone treatment. These were again subdivided into two groups: (a) a combined-treatment group to receive both a sulfone and TB-1, and (b) a group to receive TB-1 alone. The cases to be reported on here comprise 13 Europeans and 30 Bantus. Six of them were of the tuberculoid type, the rest were lepromatous.

The plan had to be modified considerably during the course of the work. At the end of the first 6 months the European patients complained that they noticed only slight clinical improvement, and I saw no bacteriological improvement; so, in April 1951, all of the Europeans were transferred to combined treatment. At later stages the other patients on TB-1 alone also asked for combined treatment, and this was not refused.

In February 1953 the bacteriological progress of the lepromatous cases was considered unsatisfactory, and all were placed on isonicotinic acid hydrazide (INH) in addition. The whole project was stopped in April 1954. We would have stopped sooner but for the fact that the changes observed in the morphology of the bacilli encouraged us to continue. It is well known that beaded bacilli are found in treated and untreated cases, but never to the same extent as we found in those under TB-1. This was so definite that we were able to say from the smears alone whether the patient was receiving that drug or not.

This changing of plans made the work lose most of its value as an investigation of the effects of TB-1 alone in leprosy, but we have gained evidence of the lack of adjuvant effort of TB-1 to sulfones and to INH. Indeed, there is evidence that TB-1 has had an antagonistic effect on the other medicaments.

The patients had a routine monthly examination, and records were made of the following: alteration of skin lesions; presence or absence of erythema nodosum leprosum (ENL); skin and nose smears; hemoglobin estimation; ulceration; weight. The urine was routinely tested only for albumen, unless a fuller examination was called for. Signs of intolerance were recorded. White-cell counts were done monthly for the first 15 months, but as nothing significant was noted they were repeated only twice during the

next two years. Serological tests for syphilis were done on all cases before the project began and later when indicated.

The daily dosage of TB-1 was as follows: 1st week, 25 mgm.; 2nd week, 50 mgm.; 3rd week, 100 mgm.; 4th week, 150 mgm.; 5th week, 200 mgm. daily, this last being the maximum dose.

The daily dosage of the sulfone (DDS) was: 1st month, 50 mgm.; 2nd month, 100 mgm.; 3rd month, 200 mgm., this being the maximum dose.

The dosage of INH was 500 mgm. daily.

The drugs were given for 6 days a week only.

#### RESULTS

*Tuberculoid cases.*—The results in the tuberculoid cases were fairly satisfactory in that all of them were finally discharged, but improvement was slower than we would expect from sulfone alone. Three cases were discharged after two years of treatment, 1 after three years, and 2 after three and one-half years. Two illustrative cases will be described.

CASE No. 10939, Bantu female. Lesions were macules with red, raised margins and healing centers. Lepromin +. Hemoglobin, 12.6 gm. per 100 cc. White cells, 4,500. Smears, negative. Urine, no abnormality. Weight, 94 lbs. Eagle serological test, positive.

Progress: The macules became inactive within five months, but smears were occasionally positive until April 1951. The lowest white-cell reading was 2,200, in that same month; the final reading was 8,000. The patient developed a nerve abscess in August of that year, when the lowest hemoglobin reading, 11.8 gm. was obtained; the final reading was 14.0 gm. Weight remained stationary. Discharged August 1954.

Conclusion: This case resolved under TB-1 alone.

CASE No. 10947, Bantu male. This patient had macules with gray, granular margins which resolved into "flat, healed macules" within four months. Three months later, however, they became erythematous and took three months to clear up. The first positive smear from an earlobe appeared in the 12th month, and that site remained positive for four months. Sulfone was added in October 1951, and the patient was discharged in December 1952.

Note: TB-1 did not stop the development of bacteriological positivity, or reactivity in macules.

*Lepromatous cases.*—The results in the lepromatous cases must be regarded as unsatisfactory. It is true that clinical improvement occurred in practically all of them, but the only real yardstick in the evaluation of a drug in leprosy is its effect on the bacilli. Only 4 out of 37 cases were rendered negative, but all of these had been taking sulfones, three for six years and the other for three years.

We use the following method of evaluating the degree of positivity (or index) of a slide:

- 4+, very numerous bacilli, hundreds to a field;
- 3+, numerous bacilli, 20-100 to a field;
- 2+, fairly numerous, 10-20 to a field;
- 1+, scanty, fewer than 10 to a field.
- VS, very scanty, fewer than 10 to a slide.
- Negative. No acid-fast bacilli in 50 fields.

At the commencement of the project the total of the indices of the 37 cases was 102. At the end of the project the total was 59.

Erythema nodosum leprosum (ENL): This condition occurred in all

but 11 of the lepromatous cases. We were not able to determine if the reaction aided the elimination of the bacilli or not. From previous experience I can say that this reaction does not occur in lepromatous cases rendered negative, nor does it ever occur in tuberculoid cases, no matter how positive their smears may be. This experience was confirmed in the present work.

**Clinical improvement:** This was evident within three months in some cases, and was marked in most cases within a year. Plaques in particular resolved rapidly, and so did macules, but nodules persisted although they softened. All infiltrations subsided to the degree where the overlying skin became like "crushed tissue paper," but in most cases complete resolution did not occur. Lepromatous ulceration of the limbs healed in five cases, persisting in one. Laryngeal ulceration healed in all of three cases. Nothing significant emerged as regards the hemoglobin or white cells.

**Toxicity:** Practically every patient showed albumen in the urine during the period, but not to the extent of causing cancellation of the treatment. Two cases showed transient jaundice. Agranulocytosis did not occur, perhaps due to the slow induction of the drug.

#### GENERAL PROGRESS

Three illustrative cases will be described.

CASE No. 10944, Bantu male. A lepromatous case with no previous treatment. On TB-1 alone for 28 months. At commencement of treatment patient had diffuse infiltration of the face, with superimposed discrete nodules. Smears were graded 4+. Lepromin reaction, negative. Urine and Kolmer test, negative. White cells, 7,150. Weight, 124 lbs. No ENL. After 4 months the discrete nodules were smaller and softer. After 2 years, ENL started and still persists. In the 28th month the smears were 3+, and DDS and INH were added to the TB-1. At the end of the experiment, 14 months later, the smears were still 3+ and the infiltrations persisted.

Comment: Two years and four months of TB-1 followed by 14 months of combined treatment did not cause improvement of this patient's leprosy.

CASE No. 8329, Bantu female. Lepromatous, previously treated with diamidin for 28 months. At commencement of the combined TB-1 and diamidin treatment the face was heavily infiltrated, and plaques and ENL were present. A smear was 4+. Urine, free from albumen. White cells, 13,000. After 18 months, DDS was substituted for diamidin, and 9 months later INH was added. At the conclusion of the experiment the plaques had resolved, ENL persisted, the face was still heavily infiltrated, and the smear was 2+.

Comment: Combined sulfone and TB-1, with INH added for the last 15 months, did not favorably alter this patient's condition.

CASE No. 8905, Bantu male. This lepromatous case had received sulphetrone for 21½ years, but the smear index remained 3+. Sulphetrone was cancelled and TB-1 substituted. In the 28th month the smears remained unaltered, so DDS and INH were given in addition to the TB-1. Fourteen months later the smears were still 3+, so the TB-1 was cancelled.

Comment: Previous sulfone treatment followed by TB-1 and then by combined treatment did not help this case.

## SUMMARY AND CONCLUSIONS

Six tuberculoid cases were treated with TB-1, and all resolved within three and one-half years. Two illustrative cases are described.

Thirty-seven lepromatous cases were treated with TB-1 for three and one-half years, with or without adjuvant sulfones. Only 4 cases became negative. Three illustrative cases that remained strongly positive are described.

Thiosemicarbazone appears to be of value in tuberculoid leprosy. Its action is weak in lepromatous leprosy, and in combination with a sulfone the two drugs seem to be antagonistic.

## SUMARIO Y CONCLUSIONES

Seis casos de lepra tuberculoidea fueron tratados con TB-1, mostrando todos resolución en término de 3½ años. Describense 2 casos típicos.

Treinta y siete casos de lepra lepromatosa fueron tratados con TB-1 durante 3½ años, con o sin sulfonas como coadyuvantes. Sólo 4 casos se volvieron negativos. Describense 3 casos típicos que permanecieron fuertemente positivos.

La tiosemicarbazona parece ser de valor en la lepra tuberculoidea. Su acción es débil en la lepra lepromatosa, y al ser combinada con una sulfona, las dos drogas parecen ser antagónicas.