RESULTS OF ONE YEAR'S EXPERIENCE WITH TB-1 IN THE TREATMENT OF LEPROSY

SALOMON SCHUJMAN, M.D.

Chief, "E. P. Fidanza" Leprosy Service (Men's Section)
"I. Carrasco" Hospital, Rosario, Argentina

In spite of the great advances which have been made in recent years in the treatment of leprosy, both by use of the sulfone compounds and of chaulmoogra in high doses, it must be acknowledged that the problem of the therapy of this disease has not been entirely solved. For this reason many attempts are being made to perfect the present drugs and to test new ones, especially those which have been shown to have some activity against the Koch bacillus, such as streptomycin, para-aminosalicylic acid, and most recently the product commonly known as TB-1.

This drug, which is the para-aminobenzoaldehyde of thiosemicarbazone, was synthesized by Domagk and his collaborators who demonstrated its bacteriostatic action on the Koch bacillus, both *in vitro* in dilutions of 1:10,000 and 1:100,000, and in experimental tuberculosis. Later it was used in the treatment of human tuberculosis with encouraging results, according to the German investigators, who also tried it in leprosy for the first time.

The experience with TB-1 in leprosy began hardly two years ago, and the published reports on this subject have as yet been relatively very few. We review briefly the results obtained by various authors before relating our own experience with this new medicament.

Hohener (1), in 1949, because of the results obtained with TB-1 in tuberculosis and the morphological and tinctorial similarities between the Koch bacillus and *M. leprae,* used the drug in a single lepromatous case for a period of six months. Although he observed rapid regression of some lepromas, he was unable to prevent the appearance of new ones, especially during the periods when the treatment was suspended.

Ryrie (2) reported on the results obtained with TB-1 (Thiacetazone) for four months in 10 cases of leprosy, of which 2 were tuberculoid and 8 were lepromatous. Although he recognized that the time of observation was short, he recorded highly satisfactory results. One case had become both clin-

ically and bacteriologically negative in three months, and another one bacteriologically negative in one month. In his conclusions he stated that thiosemicarbazone has a more rapid action than the sulfones, besides possessing the advantage of better tolerance.

Schneider (3), having seen favorable results with the use of thiosemicarbazone in a lepromatous case in which the usual antileprosy drugs had given no results, extended his experience with a larger group of patients. He reported on the results obtained in 14 lepromatous cases treated for 9 months, and believed them to be really encouraging. He observed not only diminution and later disappearance of cutaneous and mucous membrane lesions, but also improvement in the neural changes with restoration of sensibility. He concluded that TB-1 is as active as the sulfones, and that it should have a place along with the other medications.

Vegas, Convit and associates (4) reported the results obtained in a group of 42 lepromatous patients treated with TB-1/698 (Conteben) for periods varying from 3 to 6 months. They observed beneficial effects after the second month, evidenced by fading of the patches and the beginning of lessening of the infiltration of lesions, these steadily regressing with the increase of dosage and the length of treatment. They also observed fragmentation and diminution of the bacilli. Lepra reactions appeared in 63 per cent of the cases. Considering the good tolerance and the therapeutic activity of the drug, they hoped for real benefits from this new medicament.

PERSONAL EXPERIENCE

We started our first therapeutic trials with TB-1 in leprosy about a year ago (September 1950), and our experience now comprises 14 patients of whom two are tuberculoid and the other 12 lepromatous. With the exception of one lepromatous case which was of slight advancement (L-1), presenting a single macular lesion (*mancha*), the others of that type were of moderate degree (L2) or advanced (L3). It is important to note that 11 of these 14 cases had received no previous antileprosy treatment, so it follows that the benefits obtained are to be attributed to the only medicament given them, TB-1.

Before beginning treatment, all of the patients were examined clinically, bacteriologically, histologically and immunologically, and their condition was recorded photographically. Thereafter they were checked monthly as regards their clinical,

bacteriological and hematological condition, and new photographs were taken and biopsies made when there were evident clinical modifications.

Drug employed.—In 13 of the cases we used an aldehyde derivative of thiosemicarbazone which is sold in Argentina under the name of Nuclon. It was supplied us for the investigation by the manufacturing firm of Brandt. In the remaining case we used Conteben, provided by the Bayer Company, also without charge.

Route of administration and dosage.—Because of the slight solubility of TB-1 it was given by mouth, in 50 mgm. tablets. Although in tuberculosis it is advised to be more cautious, starting with 25 mgm. and not exceeding 200 mgm. daily, nevertheless in all of our cases we started with 50 mgm. daily and increased the dose by one tablet per week until a daily dose of 300 mgm. was reached. This dose was maintained for two months, and then interrupted with a 10-day rest period. At present we are commencing to increase the dosage further, and to use longer courses.

Tolerance.—In general, it can be said that the drug is one which is tolerated quite well. In only 3 of our 14 cases, and that only in the first month of treatment, there occurred slight gastric disorders (nausea and loss of appetite), which later disappeared in spite of continuous treatment. In one case there was an exacerbation of an eczema which the patient had had for a long time. Periodical examinations of the urine showed no changes worthy of mention, and the monthly blood examinations showed reactions in only 3 cases, the hemoglobin having dropped to less than 60 per cent; in the others it was maintained between 65 and 85 per cent.

Lepra reaction during treatment.—Of the 12 lepromatous cases, which have now received this drug for from 8 to 12 months, in only 3 (25%) have lepra reactions been observed. One of these patients had a mild reaction which lasted for 2 weeks. The other two patients had reactions which were more severe, and persisted for 7 weeks, with rise of temperature that necessitated bed confinement for some days. Only in the most severe periods of these reactions was it necessary to suspend treatment, and that was resumed afterward starting with small doses which were gradually increased to the habitual one.

RESULTS OF TREATMENT

Although we have previously insisted that for the evaluation of the therapeutic action of a drug in leprosy one should consider especially its effect in lepromatous cases, we included in this experiment two cases of the tuberculoid type to study the action of the drug in this form of the disease, which is

unquestionably the most benign. We therefore give the results comparatively.

TUBERCULOID LEPROSY

Here is taken into consideration only the clinical improvement, since both cases—as is frequently seen—were bacteriologically negative before treatment. In both of them we found, at the end of the second month in one and of the third month in the other, that improvement had begun. This consisted of flattening of the infiltrated patches and tubercles, which process continued in the following months until there was total resorption after from 5 to 7 months, leaving residual trophic, pigmented or achromic areas, and in other places disappearing without trace (cf. Figs. 1 and 2). The erythematous macules, on the other hand, first began to lose their color and then subsided in a short time and left no trace. In these two tuberculoid cases all of the lesions have regressed, most of them without trace, only few of them leaving inactive residual lesions.

LEPROMATOUS LEPROSY

It should be said at the outset that in all of the 12 cases treated we succeeded in preventing the progressive evolutive process natural to this form of the disease. With regard to the improvements obtained, they will be considered separately from the clinical, bacteriological, histological and immunological points of view.

(1) *Clinical changes.*—(*a*) Skin: In most of the cases beneficial effects of the drug were observed between the third and fourth months, beginning with lessening of the thickening and then flattening of the infiltrated and elevated lesions, whether diffuse or limited as in the plaques and tubercles. These changes continued as the treatment was pursued (cf. Figs. 3 and 4).

After a similar length of time—before the fourth month—we also observed paling and later diminution in size and number of the erythematous patches, and the dark areas progressively disappeared. In this way we have seen in some cases, before the end of 8 months of treatment, almost total regression of large bronze-colored, diffuse patches, leaving only small lenticular elements which we expect to subside with continuation and intensification of the treatment.

So far, we have not seen appreciable alterations of the sensory and trophic disturbances, which certain authors have claimed to have achieved with derivatives of thiosemicarbazone.

In only one case as yet, the slight one with a single macule, has there been total disappearance of the condition; in none of the other 11 cases, although evidently benefited because of the decrease and regression of the lesions, has there been total clinical clearing—and it may be added that this does not occur, after the same length of treatment, with either the sulfones or chaulmoogra.

(*b*) Nasal mucosa: The derivatives of thiosemicarbazone used first arrest and then cause regression of the lesions of the nasal mucosa. This is evidenced first by decrease of nasal obstruction, and clinically by disinfiltration of the mucosa, cicatrization of erosions and ulcerations, disappearance of crusts, and flattening and diminution of tubercles.

(2) *Bacteriological changes.*—Within approximately the same time as the clinical improvements were observed, bacteriological improvement was also found, shown first by morphological and tinctorial alterations and later by diminution of the numbers of bacilli. The morphological and tinctorial changes were found especially in the cases which had not had any previous medication, and in which there had been an almost absolute predominance of homogenous rods.

With the treatment, there was fragmentation of the bacilli and the appearance of diplobacillary and granular forms, while there was a decrease of evident homogenous forms. The tinctorial alterations consisted of decrease of acid-fastness and the appearance of bacilli which do not hold the fuchsin and present a bluish color (cyanophilic forms). With continued regular treatment there later occurred decrease in the numbers of the bacilli.

Thus, within a year of this treatment, we have been able to reduce strongly positive (4-plus) cases to 2-plus; but we have not succeeded in making them bacteriologically negative with the exception of the one slight (L1) case. At the beginning of treatment there were found in that case only scarce homogenous bacilli, and the smears made in the last three months have been negative.

(3) *Histological changes.*—In the biopsies made of the leprous tubercles or infiltrations which became flattened and disinfiltrated during the treatment, there were observed evident diminution of the infiltrative elements, and especially the vacuolization and atrophy which has been observed and described

by the majority of writers in cases benefited by sulfones and by chaulmoogra in high dosage (Figs. 5 and 6).

(4) *Immunology.*—In none of our lepromatous cases, in spite of the clinical and bacteriological improvement, have we seen any modification of the immunological condition. The lepromin reaction continues negative in all of them.

In summary.—Of these 12 lepromatous cases, it is to be said that 100 per cent of them have been benefited, the improvement marked in 2 (disappearance of most of the lesions), moderate in 7, and slight in 3. In the 2 tuberculoid cases the benefit has been marked, since all of their lesions have subsided, most of them without leaving traces.

SUMMARY AND CONCLUSIONS

In this report are described the results obtained in approximately one year of the use of TB-1 in a group of 14 patients, 2 tuberculoid and 12 lepromatous. Of this total, 11 had received no previous antileprosy treatment.

Both of the tuberculoid cases have improved markedly. All of those of the lepromatous type have improved, markedly in 2 instances, moderately in 7, and slightly in 3, the clinical and bacteriological changes being taken into consideration in assessing the degree of improvement.

It is pointed out that, with the exception of one slight lepromatous case with a lone patch which became clinically and bacteriologically negative, clinical and bacteriological clearing up has not yet been achieved.

Attention is called to the good tolerance of TB-1, since in no case has it been necessary to suspend the treatment definitively. On the basis of these facts, the following conclusions are drawn:

1. The aldehyde derivatives of thiosemicarbazone (TB-1) possess an indubitable therapeutic activity against all forms of leprosy, an activity which is evidenced by alterations and then regressions observed clinically and bacteriologically.

2. Because of the good tolerance of this drug in the great majority of cases, and its ease of administration, it deserves to be included in the therapeutic armament against leprosy.

RESUMEN Y CONCLUSIONES

En el presente trabajo el autor relata los primeros resultados que ha obtenido en un año aproximadamente con el empleo del T.B.1. en un grupo de 14 enfermos de lepra (2 tuberculoides y 12 lepromatosos), de los cuales 11 no habian recibido ninguna medicación antileprosa antes.

Señala tambien que no solamente las formas tuberculoides sino que tambien todos los casos lepromatosos se han mejorado, siendo esa mejoría muy marcada en el 16 por ciento, evidente en el 58 por ciento y discreta en el 26 por ciento, habiendose tomado en cuenta para clasificar el grado de majoría, los beneficios clinicos y bacteriologicos constatados.

Recalca que a excepción de un solo caso lepromatoso leve (L-1) con mancha unica que se ha negativizado clinica y bacteriologicamente; en los 11 restantes no se ha logrado todavía un blanqueo clinico ó bacteriologico.

Llama la atención sobre la buena tolerancia del T.B.1. ya que en ningun caso se ha visto obligado a suspender definitivamente la medicacion.

Y es en base a esos hechos mencionados que llega a las conclusiones siguientes:

1. Los derivados aldehidicos del thiosemicarbazone (T.B.1.) tienen una indudable actividad terapeutica en todos las formas de lepra; actividad que se traduce por las modificaciones y luego regresiones clinicas y bacteriologicas constatadas.

2. Dada la buena tolerancia de esa medicacion en la gran mayoría de los casos y la comodidad para su administración, merece ser incluida en el arsenal terapeutico de la lepra.

REFERENCES

1. HOHENER, K. Ein Behandlungsversuch der Lepra mit dem Thiosemicarbazon TB-1/698. Med. Klin. **44** (1949) 1378-1381.
2. RYRIE, G. Thiosemicarbazone in the treatment of leprosy. Lancet **2** (1950) 286-287.
3. SCHNEIDER, J. État actuel de l'expérimentation de nouvelles therapeutiques de la lèpre. (Thiosemicarbazone—Suspensions huileuses de DDS.) Rev. brasileira Leprol. **18** (1950) 186-205.
4. VEGAS, M., CONVIT, J., ANTONIO MEDINA, J. and DE BLOMENFIELD, E. Thiosemicarbazone (TB-1) in the treatment of leprosy; preliminary communication. Internat. J. Leprosy **18** (1950) 451-455.

DESCRIPTION OF PLATE

PLATE 1.

FIG. 1. Tuberculoid case, before treatment.

FIG. 2. The same patient after 7 months of treatment with TB-1. The lesions commenced to improve in the third month, and have now completely receded.

FIG. 3. Lepromatous case, before treatment. No previous medication.

FIG. 4. The same patient after 10 months of treatment with TB-1.

FIG. 5. Biopsy of an elevated lepromatous tubercle. Note the intensity of the infiltration. Bacteriologically 4-plus, with globi in all fields.

FIG. 6. Biopsy of a flattened tubercle and of atrophic skin in the same patient, after 7 months of treatment. Note the diminution of the infiltrate. Bacteriologically 2-plus.

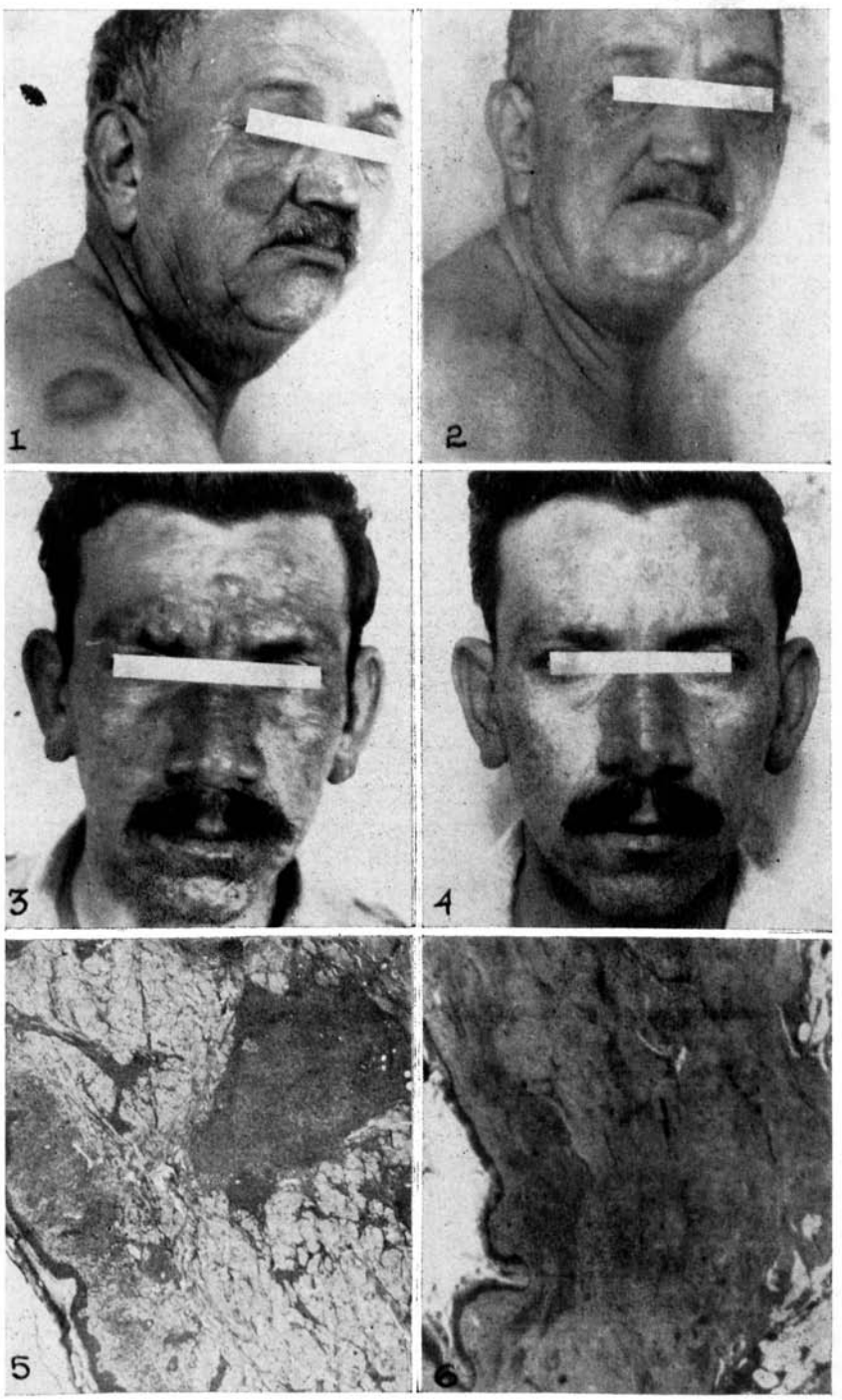

PLATE 1.