Lampren 30.320 (B.663 Geigy) was synthesized in 1954 by Barry, Belton, O'Sullivan and Twomey (1), and studied by Tschumper, Tirona, Rayanan and Bruhin (12) in 1958 at the Geigy Basle Research Laboratories. Chemically it is a phenazine derivative, specifically a riminophenazine dye of empirical formula C$_{21}$H$_{22}$Cl$_2$N$_6$ and structural formula as shown in Fig. 1. Its active substance is a red and highly stable crystalline powder. It is not water-soluble, but is soluble in such organic solvents as dimethylsulfoxide, ethanol, acetone and dioxane. Its antimicrobial properties are particularly effective against mycobacteria; the most sensitive are M. tuberculosis, M. bovis, M. ulcerans, M. balnei, and M. leprae. The latter investigators found also a synergistic action in combination with isoniazid.

Absorption and Metabolism. As the active part is a dye, it is easy to assess it by colorimetry in organic liquids, organs and extracts of organs. Until now there has been no single clinical trial that might serve as a control in ingestion of the drug. The exact absorption mechanism is still unknown. According to the data available so far, the substance enters the circulation slowly, but from there it passes rapidly into the organs, where it is incorporated particularly in the cells of the reticulo-endothelial system.

In pregnant animals (mice, rats, guinea-pigs and rabbits) it was noted that the substance hardly passes through the placenta into the fetus. The concentration observed in mother's milk is higher.

Its elimination is also slow in human organs. Because of its solubility, the only feasible way of administration is by mouth. It can be seen that the active substance, in the form of crystals, is absorbed at a rate of 50 per cent. In the form of an oily suspension, approximately 85 per cent of the quantity administered is absorbed. The form of presentation in Lampren (Geigy), an oleaginous suspension (paste) in gelatin capsules, permits an absorption of 70 per cent.

Toxicology. An acute toxicity was seen in rats, mice, and guinea-pigs. The rate was controlled in rats and monkeys for a six month period; the tolerance was very good.

**REVIEW OF CLINICAL TRIALS**

The first observations were made by Browne and Hogerzeil (7) in 1962. In 18 Hansenians treated with B.663 in a dose of 5 mgm./kgm. DDS or Ditophal, given over a period of six months, an evident action in lepromatous leprosy, both clinical and bacteriologic, was observed without any apparent symptom of toxicity, except for some hyperpigmentation. In 1965, some 44 patients had been treated. In these cases the dose was reduced to 100 mgm. per day and exhibited no variation in the bacteriologic
and morphologic indexes. In one case only a subacute nodular erythema, which was attributed to anti-inflammatory action of the medicament, occurred. In 1966, in ten corticodependent patients treated with daily doses of 100-200 mgm., reactions were controlled; steroids could be reduced gradually. In 1967 leprosy reactions were prevented by means of a dose of 300 mgm. per day.

In 1967 Pettit, Rees and Ridley (8) treated three patients affected with DDS-resistant leprosy, with B.663 in a dosage of 300 mgm per day, six days per week for a year. All of them showed some clinical, bacteriologic and histopathologic improvement. No sign of toxicity was detected, but the skin discoloration was a bewildering fact for the Chinese patients.

In the succeeding years scores of articles on Lampren treatment have appeared, emanating from all over the world. Included among these have been papers by Rostant (West Africa, 1968) (9), Hastings and Trautman (United States, 1968) (4), Warren (Hong Kong, 1968) (10), Gatti, Cardama, Balina and their associates (Argentina, 1970) (4), Devadason (Sarawak, 1969) (4), Imkamp (Zambia, 1969) (4), Schulz (Republic of South Africa, 1969) (10), and Barba Rubio, Vernon Knight, Williams and their associates (Mexico and United States, 1970) (10), to mention but a fraction of those who have contributed to knowledge in this field. The individual papers cover a wide variety of aspects of Lampren treatment in relation to clinical medicine, pathology, and neurologic and physiologic changes.

CASE HISTORIES

Our own experience is based on a total of 13 patients, comprised of four men and nine women, resident at Fontilles. The first cases were treated in 1968.

Case No. 1. J.C.M., L-type patient (male), 19 years of illness. (Fig. 2). He had been treated previously with sulfones (Promin and J-51) and hydrazides, improving, but relapsing both clinically and bacteriologically. We started B.663 treatment in May 1968. At present he has been taking this treatment for 29 months.

Initially the dose amounted to 100 mgm. per day, on a regular basis for two months. Then the dose was increased to 200 mgm. per day, and kept at that level for a month. In August 1969 we administered 300 mgm./day for two uninterrupted months. In October the dose was lowered to 200 mgm. for a few days, and afterward again set at a maintenance level of 300 mgm. daily. The patient received this dose for 15 months (until January 1970).

The bacteriology, prior to the treatment, revealed negativity in the nasal mucosa, as well as a globus and positivity in the skin. The cutaneous lesions were of the erythematous type, with diffused edge and abundant, located in the trunk, front and back areas, buttock and arms and legs. Also, some infiltrations in the legs and lower arm were observed, and in addition some eyebrow alopecia. The patient has had no lepra reaction for the last three years. In his neural alterations he presents no paralytic lesion, but some extensive thermal anesthesia and pain in limbs, face and buttock.

Clinical results. During this period of treatment, discoloration has been improved, becoming both pigmented and dis-infiltrated. The sensory alterations have scarcely varied. The general condition of the patient is good. There has also been perfect drug tolerance. The pigmentation caused by the drug commenced 15 days after initiation of treatment and decreased when the dose was lowered to 100 mgm. per day.

Bacteriologic results. The bacteriology in the nasal mucosa and skin has remained permanently unchanged in this patient.

Lepra reactions. During this period of treatment no reactional outbreak was seen.

Case No. 2. M.O.L., L-type patient (male), 2 years of illness. First treated. B.663 treatment was started in July 1968. At present he has been under treatment for approximately 18 months. The initial dose was 100 mgm. per day; he had it for approximately one month and a half. Then the dose was increased to 200 mgm. a day for 15 days, and then to 300 mgm. per day. This treatment was uninterrupted for one month. In October 1968 the dose was lowered to 100 mgm. daily for 15 months (until January 1970).
The bacteriology prior to treatment revealed positivity with a globus in the nasal mucous and positivity with two globi in scrapings of the skin. The cutaneous lesions are large, with numerous lepromas distributed through the arms, forearms, thighs and scalp. There are infiltrations in both legs, face and ears, and ulceration in the right leg lower area. There is almost total alopecia of the eyebrows, and there are osteo-articular trophic lesions in both feet and ulcerations in the soles of the feet. The nervous system presents the typical alterations of sensitivity in lesions in the arms, forearms and legs. There are no limb paralytic alterations.

**Clinical results.** During this period of treatment the patient has not exhibited any alterations, with the exception of occasional hand and foot edema. The cutaneous discoloration, which was very marked, decreased when the drug dose was lowered. The lepromas have been fully resorbed. The covering skin was atrophic, umbilicated, and more pigmented. The scalp lepromas, much improved and in regression, have not disappeared fully. Closing of the leg ulceration took place two months later.

**Bacteriologic results.** The bacilloscopic improvement of this patient has been very satisfactory. The nasal mucosa has been negative for 15 months and the skin shows...
real improvement in the morphologic and bacteriologic indexes.

*Lepra* reactions. During the period of treatment no reaction outbreak has been observed.

Case No. 3. F.B.G., clinical L-type patient (female); treatment for the first time. Since September 1968 she has been under B.663 treatment. The dose initially given amounted to 100 mgm. per day; because of the appearance of various reactional outbreaks, it was increased to 200 and 300 mgm. daily. In three reactional outbreaks and with an increased dose of B.663, after a cautious period of time to assess the effect, a combination with thalidomide was found to be necessary, and the dose of B.663 was decreased to 100 mgm. In a reactional outbreak the clinical picture was solved only by increasing the dose of B.663 to 200 mgm. a day. From November 1, the patient received 300 mgm. per week. The bacteriology prior to the treatment revealed an intense positivity of the nasal mucosa with a globus and with two globi and one positive in the skin.

The cutaneous lesions include lepromas in the face, thighs, legs and forearms, some erythema-pigmentary discoloration in the thighs, infiltrations in the face and limbs, and some alopecia of the eyebrows. The neural lesions are alterations of heat and pain sensitivity in the limbs, and cutal and external sciatric-popliteal reactional neuritis.

**Clinical results.** Clinical improvement is evident, manifested by regression and disappearance of the nodular lesions, as well as face and ear dis infiltrations. Improvement with respect to the sensory alterations observed has been distinct.

**Bacteriologic results.** Negativization of the nasal mucosa was observed at 14 months, as well as improved skin morphologic and bacteriologic indexes.

*Lepra* reactions. Four reactional outbreaks occurred during the treatment. The first was an acute lepra reaction in the second month of treatment, with multiple nodular erythematous lesions, algeas, cervical adenopathy and a temperature of 39-39.5°. The dose of the drug was increased to 300 mgm. over a period of 10 days. As little improvement in reaction occurred, thalidomide was used. This actually caused the reaction to disappear and the dose of Lampon was lowered to 100 mgm. a day. After four months a new outbreak of lower intensity than the previous one took place and, therefore, the dose of B.663 was increased to 200 mgm. daily. The use of thalidomide also proved necessary. A new but weaker outbreak took place two months later, but disappeared completely on increasing the dose to 200 mgm., but this time without thalidomide treatment. Eight months later, a new reactional incident presented. It gave rise to a few new lesions and reactivation of some old ones. The patient was treated with thalidomide again.

Case No. 4. S.A.P., clinical L-type patient (female). Two years of illness and treatment for the first time. (Fig. 3). B.663 treatment was started in August 1968 and thus, at present, she has been under treatment for 17 months. The dose was 100 mgm. daily for 14 uninterrupted months. It was decreased to 300 mgm. weekly in October 1969; she continued to have this for three months. The bacteriology prior to treatment revealed some positivity in the nasal mucosa (a globus) and skin (2 globi and 3 positives). The cutaneous lesions included erythema-pigmentary discoloration distributed over three or four parts of the face, as well as an abundance of lepromas on the chest, abdomen, back and limbs. There were extensive infiltrations in the face and hands and, finally, some residual scars. In the neural system sensitivity to heat and pain was altered in the face and limbs, and there were paresthesias.

**Clinical results.** Perfect tolerance. Increased skin pigmentation and cutaneous lesions. Face discolorations seem more pigmented, but in regression. Lepromas have appeared again. Some have completely disappeared, leaving scars. Great improvement in infiltrations.

**Bacteriologic results.** As far as bacilloscopy is concerned, highly improved morphologic and bacteriologic indexes were observed.

*Lepra* reactions. The patient presented a small reactional outbreak accompanied by
FIG. 3. Case No. 4, L-type patient, 2 years of illness. a, extensive infiltrations in face. b, improvement 1 year later after Lampren treatment. c, leg ulcerations. d, improvement 13 months later.
nodules in the arms and back, which did not give rise to fever.

Case No. 5. C.L.G., L-type patient (female). Six years of illness; treatment with J-51, DDS and Ciba 1906. Prior to her admittance to this sanatorium after a year and a half of continued lepra reaction, she was treated with prednisone. B.663 treatment was started in June 1968, and accordingly the drug has now been administered for 16 months. The initial dosage was 100 mgm. daily for one month. Then it was increased to 200 mgm. daily for an additional month, and later to 300 mgm. for another month. The dose was lowered to 100 mgm. daily in October 1968, at which rate it was continued for 13 months. At the end of that period, the dose was reduced again to 300 mgm. per week.

The bacteriology prior to treatment was negative in the nasal mucosa and positive in the skin (two globi and granulations). The patient presents such lesions as infiltration of the arms and legs, erythematous-pigmentary discolorations in the face and alopecia of the eyebrows, as well as a great many nodular and some polymorphous erythematosus elements. The neural lesions were of the reactional hypertrophic type accompanied by severe pain.

Clinical results. When admitted to our sanatorium in May 1968, the patient was affected by a severe and extensive general lepra reaction, with the serious additional problem of previous treatment with corticosteroids for a year and a half. She was given thalidomide as a reactional and symptomatic treatment at the rate of 300 mgm. daily in order to obviate the corticosteroid dependence. The lepra reaction lasted for 30 days; the fever disappeared ten days after treatment was started. Corticosteroid treatment was progressively decreased. Thus, under these "reactional status" conditions, B.663 treatment was started in June 1968 at a dose of 100 mgm. per day or even 200 mgm. As far as the clinical results are concerned, we shall first point out that the reactional status was overcome in two months' time; the steroids were removed and Lamprén and thalidomide treatment was undertaken simultaneously. Since then, no reactional inci-
present she has been under this treatment for 21 months. The initial dose was at the rate of 100 mgm. per day for approximately two months. Then the dose was raised to 200 mgm. per day for one month, then again increased to 300 mgm. per day for three months, and afterward lowered to 100 mgm. per day in October; this dosage has been administered for 15 months regularly.

The bacteriology prior to treatment revealed an acute positivity in nasal mucosa and skin. The cutaneous lesions are lepromas located in the arms, forearms and face, and there are forearm and leg infiltrations. The neural lesions were in the lepra reactive phases and were of a neuritic type. In addition there was some alteration in heat and pain sensitivity.

Clinical results. After previous experience with reactive phases, accompanied by high temperatures and neural pain, these lepra reactions were corticosteroid-treated—the patient has shown no reactive outbreak at all during the B.663 treatment, except for a few nodular erythematous type elements. The infiltrative and nodular cutaneous lesions have appeared again.

Bacteriologic results. There has been remarkable mucous and skin improvement. The nasal mucosa has become negative during the months of treatment. The patient shows a good general state and perfect drug tolerance. The discoloration has been modified according to the dose used; the higher the dose the stronger the pigmentation and vice versa.

Lepra reactions. During the treatment period no lepra reaction occurred.

Case No. 8. J.G.R., clinical L-type patient (female). Thirty years of illness. Previously given some specific treatment (Diosone, Promin, and DDS). B.663 treatment was started in September 1968 and continued for ten months. The initial dose was at the rate of 100 mgm./daily for exactly one month. Then the dose was decreased to 300 mgm. a week for nine months. Afterward the medication was discontinued.

Case No. 9. R.C.B., clinical L-type patient (male). (Fig. 4). Two years of illness; no pretreatment. B.663 treatment, started in August 1968, has been continued for a period of 17 months. The initial dose was at a rate of 100 mgm. per day for one month. The dose was then raised to 200 mgm. for one additional month and afterward lowered to 100 mgm. daily again. This has now been administered regularly for 15 months. The bacteriology prior to the treatment was positive in the nasal mucosa and skin. The cutaneous lesions present consisted of infrequent hyperchromic discolorations on the left leg, and face infiltrations. There were also some discrete areas of sensitivity dissociation in the left leg and right arm.

FIG. 4. Case No. 9, clinical L-type patient (male), 2 years of illness, no pretreatment; a, infiltration (right arm). b, improvement 11 months later.
Increased cutaneous and macular pigmentation has been noted. The general condition is good and there has been perfect drug tolerance as well.

**Bacteriologic results.** Bacilloscopy has been satisfactory, amended particularly in the nasal mucosa, which became negative within eight months. Skin improvement is evident.

**Lepra reactions.** Neither prior to nor during the treatment has any lepra reaction been observed.

**Case No. 10. M.R.M., clinical L-type patient (female).** Thirteen years of illness, previously treated (Procin, Diasone, and J-51). Sulfone-resistant. B.663 treatment was started in November 1968. The patient has now been under treatment for 14 months. The initial dose was administered at the rate of 100 mgm. daily for 11 months. In October 1969 the dose was lowered to 300 mgm. weekly for three more months. Bacilloscopy prior to the treatment revealed acute nasal mucosa and skin positivity. Cutaneous lesions consisted of an abundance of lepromas situated on the limbs, as well as many erythematous pigmentary discolorations on the back and thighs and infiltrations of the legs. Neural lesions included bilateral ulnar-median paralysis and ulcerating trophic lesions of the soles of the feet.

**Clinical results.** This case, which previously exhibited some corticosteroid-treated severe general lepra reactions, has shown substantial clinical improvement, and it is to be emphasized that no further reactional outbreak has occurred. Also, increased cutaneous and macular pigmentation has been observed. On the other hand, many of the lepromas have become resorbed and infiltrations have improved.

**Bacteriologic results.** Bacilloscopy revealed remarkable nasal mucosa improvement. No changes were noted in the skin.

**Lepra reactions.** During the treatment no additional reactional outbreak has been observed.

**Case No. 11. M.G.N., clinical L-type patient (female).** Twenty years of illness. Previously treated with J-51. B.663 treatment was started in January 1969, and thus the patient has now been under treatment for 12 months. The initial dose was at the rate of 100 mgm. per day for eight months; then it was lowered to 300 mgm. per week for four more months.

The bacteriology prior to the treatment was negative in the nasal mucosa and positive in the skin. Cutaneous lesions consisted of a large number of erythematous discolorations, clearly located on the face, trunk, back, buttocks, thighs and limbs, and of diffuse edge type. Neural lesions consisted of ulnar paralysis.

**Clinical results.** The patient commenced B.663-treatment in the course of an extensive and acute reactional outbreak. This disappeared a short time afterward, and since then, the treatment period, it has not recurred. It is worth noting that the discolorations originally observed have changed in character, becoming more pigmented and diffused. The patient's general condition is good; during the treatment both pregnancy and parturition have been normal. The fetus did not show very marked pigmentation.

**Bacteriologic results.** Nasal mucosa bacilloscopy has not changed, remaining negative. In the skin, it has slightly improved.

**Lepra reactions.** No reactional incident has been recorded.

**Case No. 12. A.S., clinical reactional tuberculoid type patient (female).** Three years of illness. Previous specific treatment with sulfones (DDS for 2 months). B.663 treatment, started in October 1969, has been continued for four months. The dose given initially amounted to 100 mgm. per day for one month; the dose was then decreased to 300 mgm. per week for two more months.

Bacilloscopy prior to the treatment was positive in the nasal mucosa and skin. The cutaneous lesions present consisted of infiltrating erythematous-pigmentary discolorations in the face, back, buttocks, limbs, palms of the hands and soles of the feet. There was also edema of the face and hands. In addition there were heat and pain alterations in the lesions and forearms and legs.

**Clinical results.** The patient entered the sanatorium showing a reactivation of the
above named discolorations, algies and neuritis. She received thalidomide, and, once this clinical picture had been overcome, B.663 at an initial dose of 100 mgm. per day; this was lowered to 300 mgm. per week. The patient's general condition is good. In spite of the short-term treatment, increased coloration of the face and larger pigmented macular lesions are seen. There has been improvement and disinfiltration of her macular lesions, with regression at the edges and more extensive pigmentation.

Bacteriologic results. Bacilloscopy has shown a satisfactory modification in the nasal mucosa, which became negative in three months, while stationary in the skin.

Lepra reactions. No reactional incident was observed during the treatment period.

Case No. 13, J.F.F., clinical L-type patient (male). Two years of illness. First treatment when he entered our sanatorium. B.663 treatment was started in May 1968, and continued for six months only because he left the sanatorium. The initial dosage amounted to 100 mgm. per day for four months. At the end of this period, in May 1968, the dose was lowered to 100 mgm. daily. He continued to have this dose until leaving our sanatorium.

Bacilloscopy prior to the treatment was negative in the nasal mucosa and positive in the skin. Cutaneous lesions consisted of face, arm and leg infiltrations, and scars and trophic-osteoarticular lesions in both feet.

Clinical results. During the six months' observation of the B.663 treatment, the patient showed clinical and bacteriologic improvement. The tolerance was perfect. There was no further lepra reaction with the exception of some algie of the feet and hands.

Bacteriologic results. In spite of the brevity of treatment there was some skin bacilloscopic improvement. The nasal mucosa continued to be negative.

CONCLUSIONS

Our experience covers 13 patients, comprised of four males and nine females, and 12 lepromatous and one reactional tuberculoid case (Table 1). The treatment period ranged from four months (Case No. 12) to 21 months (Case No. 7). Except for Cases 12 and 13, the experience corresponded to an observation period exceeding one and a half years.

Drug doses have been altered during the research period. At the beginning, doses were at the rate of 200-300 mgm. per day, but they were lowered to 100 mgm. per day.

Table 1. Summary of 13 Cases.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Spec.</th>
<th>Duration of Disease</th>
<th>Treatment</th>
<th>Duration of Treatment</th>
<th>Bacilloscopy</th>
<th>Arteries</th>
<th>Mucosa</th>
<th>Skin</th>
<th>Palmar</th>
<th>Mucosa</th>
<th>Skin</th>
<th>Nerve</th>
<th>Lowered</th>
<th>S.R.</th>
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<td>1 month</td>
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<td>15 months</td>
<td>200 mg</td>
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<td>15 months</td>
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<td>L.</td>
<td>14 months</td>
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<td>15 months</td>
<td>1 month</td>
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<td>4 months</td>
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<tr>
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<td>L</td>
<td>2 years</td>
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<td>6 months</td>
<td>100 mg</td>
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day after the first three months. At present seven cases (Nos. 3, 4, 5, 8, 10, 11 and 12) are treated at the rate of 100 mgm. on an every two day basis. The others are treated at the rate of 100 mgm. drug per day.

**Clinical results.** All cases have improved from a clinical point of view. Macular infiltrative and ulcerative lesions have returned. Improvement and disappearance of lesions are in a direct relationship with the treatment-time involved. Nodular lesions have reacted more quickly than macular infiltrative ones. In this respect, reference is made to Case No. 2 showing a total resolution of lepromas. These were exhibited also in the scalp, and disappeared completely in Cases Nos. 3, 4, 7 and 10. Also, the specific ulcerations, and the ulcerated nodules in particular, reacted quickly. The rhinopharyngeal mucosa also improved parallelly with the cutaneous lesions. Sensory reactions have improved, but not so quickly or to the same extent as the cutaneous ones. As far as the hypertrophic neuritis was concerned, a lower neural expansion was achieved.

**Bacteriologic results.** The following results have been obtained: The nasal mucosa became negative in five patients, i.e., Case No. 2 in the 15th month of treatment; Case No. 3 in the 14th month; Case No. 7 in the 10th month; Case No. 9 in the eighth month, and Case No. 12 in the third month. Three other cases showed some morphologic and bacteriologic index improvement. In the other cases except for Case No. 12, which was negative, all patients were highly positive. Clear improvement was seen in the morphologic and bacteriologic indexes in 10 cases; those indexes were stationary in three cases.

**Tolerance.** We can say for certain that lepra reactions are much less frequently observed than in sulfone treatment. Case No. 3 has suffered during the 16 months' treatment from four reactional incidents; one of these was rather acute, being accompanied by high temperature, adenopathies, nodular erythema, etc. As no improvement was experienced by raising the Lamprén dose to 300 mgm. daily, thalidomide was administered and the reaction disappeared. The other outbreaks were less severe, and in one of them, the reaction disappeared completely when the dose of B.663 was increased to 300 mgm.

In Case No. 4 some elements of skin erythema appeared, which actually called for no treatment. The same applies to Case No. 7. Prior to the treatment Case Nos. 7 and 11 experienced some repeated and continued corticoid-treated lepra reactions. These have exhibited no acute outbreak during our experience based on Lamprén.

The general tolerance has been good in all cases. We should note the appearance of enteritis, a phenomenon of minor importance, in some patients.

Case No. 8 suffered from diabetes, which has not been modified. Pregnancy occurred in Case No. 11; the child was born perfectly and showed no pathologic discoloration. In addition to the typical pigmentation, which appears in the course of this treatment, we can state that it occurs between 10 and 20 days after starting the treatment. The discoloration is severe at a dose of 300 mgm. per day, but when it is lowered to 100 mgm. three times per week, it is substantially reduced.

In our opinion, Lamprén is an active medication in the therapeutic field of leprosy. It shows evident efficiency, both from a clinical and from a bacteriologic point of view. Clinical improvement is quicker; Tolerance to the drug is very good, showing a significant advantage over the sulfones. Reactional incidents are much less frequent. We trust that on the basis of wider observation, we will manage to achieve total clinical-bacteriologic inactivation.

**SUMMARY**

We obtained our results in a group of 13 patients (4 males and 9 females) composed of 12 lepromatous and one tuberculoid case in reaction. The duration of treatment was from four to 21 months. The observation period was less than a year and a half in 10 cases. The dosage was varied in the course of the follow-up examinations. The initial doses were 200-300 mgm. daily, which could be reduced to 100 mgm. after the first three months; 7 cases were treated...
with 100 mgm. alternately.

Clinical improvement was observed in all patients with macular lesions, nodules, infiltrations and ulcers. The rhinopharyngeal mucous changed for the better correspondingly, whereas alteration in sensory perception improved more slowly. Five patients became bacteriologically negative (nasal mucosa). In 10 patients we observed a clear morphologic and bacteriologic improvement of the skin. Reactions were rare, but in one case four periods of reaction were noted, only one of which was intense.

Tolerance to the drug was very good. Between the 10th and 20th day of treatment all cases showed typical reddish pigmentation, which grew less when the dose was reduced.

REFERENCES


