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LEPROSY REVIEW

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CONTENTS

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EDITORIAL

1. Trial of a New Drug ("B 663") in Leprosy:

In this issue (page 6) will be found a report by S. G. Browne and L. M. Hogerzeil on their trial in leprosy of a synthetic Rimino-compound derived by progressive chemical alteration of the anilino-aposafranine molecule. The trial of this drug was suggested by R. G. Cochrane and V. C. Barry and carried out by the authors in Uzuakoli on 16 patients. During the trial all patients developed a ruddy skin and some became hypermelanotic but there were no signs of serious toxicity. The results were encouraging, because all patients, whether given "B 663" alone or combined with DDS showed considerable improvement in the lepromatous clinical condition, and the reduction in the bacterial index was also marked. There was a 49% reduction in patients treated with DDS as well as "B 663". There was 28% reduction in patients treated with "B 663" alone. Some patients were given ditophal in addition to "B 663" but the results here were sometimes good and sometimes negative and the results of the addition of ditophal must be regarded as capricious. This preliminary report by S. G. Browne and L. M. Hogerzeil suggests a valuable new line of investigation in the drug therapy of leprosy.

2. Three Reports on Etisul

It will be noted in this issue that there are three reports on Etisul each coming from widely distant regions of the world, viz. Y. F. Chao from Taiwan, V. Ekambaram and C. S. Gangadhar Sharma from India, and K. F. Schaller and C. Serié from Ethiopia. It is possible to detect from all these authors a certain consensus of opinion as to a greater efficacy and a greater rapidity of action of this drug in their experience.

3. Further Reports on DPT (Ciba 1906)

Of much interest in this issue is the report by F. Kradolfer and K. Schmid on the possibility of injectable DPT. Also in this issue R. M. Wilson, J. S. Kim, and S. C. Topple give a report on the use of DPT in leprosy cases who had shown lepra reactions. These authors studied 33 such cases altogether and had a good response in a third of them from the use of DPT.

4. Plantar Ulcers

It is fortunate for leprosy patients with deformities that in the past two or three years more and more attention is being given to their problems with very good results. We are glad to publish in this issue a study by W. F. Ross on the Etiology and Treatment of

Plantar Ulcers. Recently E. W. Price had a series of papers on this subject in *Leprosy Review* 1959, 30, 2, 98; 30, 3, 180; 30, 4, 242; 1960, 31, 2, 97; 31, 3, 159.

5. By courtesy of Dr. B. D. Molesworth of Ghana we are able to give the following account of the WHO Regional Leprosy Conference—Europe and Eastern Mediterranean.

This was held at Istanbul from the 2nd to the 7th October, 1961, in the Hall of the Professors—Faculty of Medicine of Istanbul.

After the introductory Session the subjects chosen were:

(i) The Extent of the Problem in the Area
(ii) Treatment
(iii) Teaching and Training
(iv) Leprosy Control
(v) Prophylaxis
(vi) Rehabilitation.

The general form of the Conference was the same as those previously held in the other Regions. Namely papers were prepared by WHO (consultants and temporary advisers) on the various subjects and these were then discussed by the delegates and observers.

On the whole a remarkable amount of agreement was achieved considering the enormous differences in the problem presented by the various countries; one with only six known cases and some with an estimated number of 25 to 30,000.

Obviously with such differences the approach of the countries differed too, with regard to isolation and staff and facilities. Likewise case finding methods must be entirely different. Sample areas and checking of contacts in its widest sense being more suited to countries of low incidence with a small problem than more wasteful mass campaigns.

Special attention could be given to infected zones within a country.

It was decided a specialised leprosy service was of value where the problem warranted it—this service to be part of the State Service, preferably under a chief with public health training, and working through all existing and available health structures.

A small leprosy advisory Committee to advise the Government was considered good.

It was recommended that there was no need for special legislation for leprosy and old laws should be abandoned to bring it into line with modern ideas.

The same criteria of arrest were adopted as at Brazzaville and Tokyo.

Treatment: DDS either oral or with "retard" injections remained the first choice for routine treatment; and for individual treatment

DPT Ethyl Mercaptan and Sulpha methoxypyridazine were included, though it was appreciated dosage and choice of drug would be modified by local conditions.

Reactions: In mild reaction it was decided treatment need not be interrupted but it might be necessary in severe types. The underlying cause should always be sought and treated. Useful agents cited were calcium preparations, blood or plasma transfusions, and corticosteroids preferably given over short periods and tapered off rapidly—a dosage equivalent to 20–30 mgm. of prednisolone daily at the start.

General measures should not be forgotten including the prevention of contractures during acute episodes. Drug trials should be conducted on lepromatous cases and if possible on cases hitherto untreated, using as a control group those on standard DDS treatment.

An attempt should be made to match the two groups with regard to age, sex, duration and severity of the disease.

Sufficiently large groups for correct statistics and to last for at least one year; laboratory control should be as laid down by WHO in their document "Controlled Clinical Trials in Leprosy" (WHO/PA/77.60).

Prophylaxis: All agreed that compulsory segregation was a hindrance to control and that other methods were proving more efficacious and that separation of children from parents should be limited to indigent or uncooperative families or during periods when parents were in hospital.

It was deemed unnecessary for special BCG campaigns since in most countries this was being carried out by tuberculosis campaigns.

Chemoprophylaxis in children with infected parents was recommended and it was pointed out that during breast feeding the child received adequate sulphone in the mothers milk (provided of course the mother was on treatment!)

After weaning a dose of 5 mgm. DDS per week per kilo of body weight was considered adequate, which could be administered in a suitable mixture.

Training in leprosy for students should be with, if possible the dermatological department in cooperation with other departments such as public health and orthopaedics. More time to be given, if possible including practical demonstrations, etc.

Short courses could be run for General Practitioners in centres with adequate cases.

Special courses longer and more detailed in countries which need specialists in leprosy.

All paramedical personnel who might be in contact with leprosy

should receive instruction to enable them to recognize cases and to assist in leprosy campaigns.

Give publicity in health education to all grades of the public.

Rehabilitation: For this field it was stressed that early and accurate diagnosis and regular treatment was the best way of avoiding deformity and consequently the need for rehabilitation.

Education of the patient to gain his cooperation was important. Prevention of deformities should be taught and surgical intervention given where necessary and finally the reinstatement of the patient as an independent member of society.

It was stressed that all existing medical and surgical facilities should be used—the patient with leprosy being treated as any others, and those concerned convinced of the possibility of this. The uses of a social service in leprosy were stressed and the re-education of the public to receive the "cured" patient back into society.

This is a very brief summary of the findings of the Conference but no report would be complete without acknowledging all the kindness and hospitality the Conferers received from our hosts both in a private capacity and as a body, including cocktail parties, a delightful dinner in a restaurant of very original character, even the Sea of Marmora and finally a delightful boat trip from Istanbul almost to the Black Sea completed a very useful as well as enjoyable work.

6. Obituary

Professor RALPH FRANCIS NAYLOR, PH.D.

We have heard with the deepest regret of the death, following a road accident in Northern Rhodesia, of Professor Naylor, on 6th August, and print this with acknowledgements to "Without the Camp."

"Dr. Ralph Naylor had very close associations with The Mission To Lepers. While he was studying in London he manifested his interest in it and considered volunteering for service in its ranks. He came to the decision that he could best serve as a "non-professional missionary", going to Makerere College in Uganda as a lecturer in chemistry, and there engaging particularly in research into the chemotherapy of leprosy. He was the Mission's representative on the Managing Board of the Kumi Union Leprosy Centre, of which the Mission is one of the four partners. He went as one of the Mission's delegates to the International Congress of Leprology at Tokyo in 1958, where he presented a Paper; and on the recent foundation of the Royal College in Kenya he was appointed to the Chair of Chemistry. Always he maintained a close and active interest in the Mission's work and helped it in practical ways, apart from the valuable research he engaged in, particularly on the

action of sulphones on the metabolism of the *Mycobacterium leprae*, thus adding to the body of knowledge about the disease, and so helping forward its defeat.

Dr. Naylor was a man of deep Christian faith, ever eager to present and interpret it at the points of greatest need. His influence among students was considerable and he will be sorely missed as a friend, a teacher, and above all as a Christian.

Our sympathy goes out to Mrs. Naylor, and her young son who was also seriously injured in the accident. We give thanks for the work and witness of this dedicated layman, whose intellectual gifts were matched by his qualities of heart; who made a very valuable contribution in leprosy research, and who in all showed himself to be a true follower of his Lord."

A.D.M.

Dr. Naylor also gave considerable co-operation in the work of the East African Leprosy Research Centre and in many branches of leprosy work in East Africa. Some of his research is reported in a paper in the October issue of *Leprosy Review* (see the paper by Ellard and Naylor) (1961) **32**, 249–258.

"B 663" IN THE TREATMENT OF LEPROSY

Preliminary Report of a Pilot Trial

By S. G. BROWNE, M.D., F.R.C.P., F.R.C.S., D.T.M.
and
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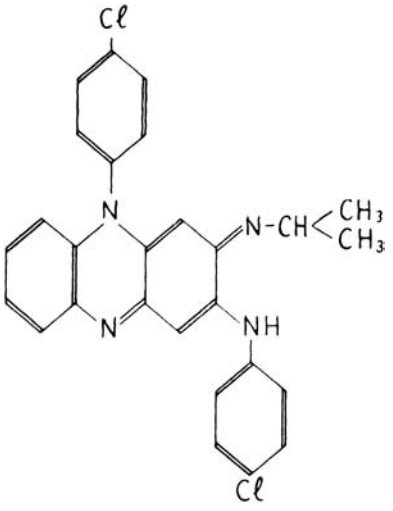
The very high anti-tuberculosis activity of many recently-synthesized phenazine dyes indicated that they might be of value in the treatment of leprosy. Dr. R. G. Cochrane (Leprosy Research Unit, London) and Dr. Vincent C. Barry (Medical Research Council, Dublin) suggested a clinical trial of "B 663" (Geigy S.A.), in many ways the most promising of the series, in a group of patients with lepromatous leprosy in Eastern Nigeria.

B 663 is a Rimino-compound with the structural formula:



The Rimino-compounds are derived by progressive chemical alteration of the anilino*apo*safranine molecule (BARRY *et al.*, 1957; DOULL, 1961). The forerunner of these compounds (B 283) has very high anti-tuberculosis activity *in vitro*, and some anti-tuberculosis and anti-leprosy activity *in vivo* (ALLDAY and BARNES, 1952; DOULL 1952).

In a series of papers, Barry and his co-workers have shown that, weight for weight, B 663 is more active in experimental tuberculosis in laboratory animals than any other substance hitherto investigated; it is the only substance known to exert a true chemoprophylactic action in animal tuberculosis. Other workers (e.g., CHANG, 1959;

ACHARYA *et al.*, 1959; STEENKEN *et al.*, 1960) have confirmed their main findings. The drug administered orally or parenterally appears to be taken up unchanged by living mycobacteria. When given in large doses, it is deposited in crystalline form in the principal organs, particularly in cells of the reticulo-endothelial system, but the slight toxicity observed seems to be limited to some foreign-body reaction provoked by the presence of these microcrystals. Adequate toxicological investigations have been carried out.

For the purposes of this investigation, the drug was supplied (by Messrs. J. R. Geigy, S.A.) in the form of orange-red micronized crystals (particles not exceeding 5μ in diameter), presented in capsules for oral administration containing 0.1g. As suggested by evidence obtained in experimental animals, a small amount of vegetable oil (1 teaspoonful of groundnut oil) was given to each patient with the daily dose of drug prescribed, to facilitate absorption from the intestine.

Choice of patients

All patients admitted to Uzuakoli Settlement just before the beginning of the trial, and suffering from lepromatous leprosy (14) or from borderline leprosy highly positive bacteriologically (2), were given recommended doses of B 663. These patients, unselected, had received no treatment before admission, but six of them, while awaiting the arrival of the drug, had received minimal doses of dapsone (0.05 to 0.1g. twice weekly) for two to eight weeks before the beginning of the trial.

Treatment

All 16 patients received a daily dose of 1, 2 or 3 capsules of B 663, each containing 0.1g. of active substance, for six days a week for six months. The amount of drug given was according to body-weight; thus,

1 patient weighing 50 lbs. received 1 capsule daily;

5 patients weighing on the average 94 lbs. received 2 capsules daily;

10 patients weighing on the average 116 lbs. received 3 capsules daily.

The 16 patients were divided into three groups:

Group 1: 3 patients received, in addition to B 663, standard doses of dapsone;

Group 2: 8 patients received no additional drug treatment. Of these 8 patients, 3 began their course of treatment at the same time, and the remaining 5 began later, the point of entry depending on the date of admission to the Settlement;

Group 3: In addition to B 663, 5 patients received daily inunction with 5 ml. of Etisul liquid formula (ditophal), kindly supplied by Messrs. I.C.I. (Pharmaceuticals) Ltd. (BROWNE, 1961). Inunction was carried out for six days a week for the first three months of the trial period.

Thereafter, patients in Group 1, and the first 3 patients in Group 2, received standard doses of dapsone alone. The remaining 5 patients in Group 2 are continuing to receive B 663 alone. The 5 patients in Group 3 are now receiving standard doses of dapsone alone.

Laboratory investigations

Smears were taken at fortnightly intervals from eight sites, and the Bacterial Index determined by the same experienced technician, who from the preparations estimated the proportions of *M. leprae* of degenerate morphology at each site. Smears were taken on at least two occasions before the beginning of treatment with B 663 to minimize errors due to the hazards of smearing and to fortuitous changes in concentration of bacilli in the dermis.

Full blood examination, including estimation of the Erythrocyte Sedimentation Rate, was performed at monthly intervals.

Full urine examination was made every fortnight.

Investigation of liver function was made every month, by means of Schlesinger's test (for urobilinogen), the Takata-Ara test, and the Thymol turbidity test.

Results

All patients supported well the drugs given, and none had to be withdrawn from the trial.

Within ten days of the start of the trial, all the patients began to develop a ruddiness of the skin, shown particularly in the less pigmented and thin skin of the face (e.g., peri-orbital), the palms and soles. Generally, it was the skin not affected by lepromatous infiltration that became ruddy. The lepromatous infiltrated skin and the lepromatous nodules became hyperpigmented, and remained so. In some patients, a progressive generalized hypermelanosis became apparent. These changes in cutaneous pigmentation were not accompanied by subjective symptoms, and appeared to have no deleterious significance. They indicated good absorption of the drug from the intestine.

The conjunctivae became slightly muddy in most patients.

A baby at the breast became ruddy like its mother, and then slightly hypermelanotic. Five months after the end of the trial, the pigmentation of the skin had returned to normal, but the baby (then aged 15 months) developed the typical hazy patches of early leprosy, bacteriologically negative.

Toxicity

No signs of toxicity have developed beyond slight transient nausea and giddiness in two patients in whom the drug/body-weight ratio was somewhat higher than the average.

Clinical results

Notwithstanding the small size of the groups, and the short period of observation, the progress made by these patients treated with B 663 appears to warrant publication of this preliminary report.

All the patients who received B 663 alone (8) or with dapsone (3), and 2 of the 5 patients who received ditophal in addition to B 663, showed considerable improvement: the size and elevation of the lepromata became markedly less, some of the smaller lenticulate nodules on cheeks and ears almost disappearing; lepromatous infiltration decreased; repigmentation of lepromatous macular areas took place, sometimes as part of a generalized hyperpigmentary process.

The greatest average clinical improvement was shown by the 3 patients who received dapsone in addition to B 663.

Of the remaining 3 patients, who had all received ditophal in addition to B 663, one was moderately improved, and two were unchanged.

Bacteriological results

Reduction in the Bacterial Index and degenerative changes in *M. leprae* ran *pari passu* with clinical improvement.

The reduction was most marked in the 3 patients treated with dapsone: viz. 49%. It was 28% in the 8 patients treated with B 663 alone. Of the ditophal group, the fall in B.I. was 65% in the 2 markedly improved patients, 19% in the patient moderately improved, and unchanged in the remaining 2 patients.

Histological studies of skin sections, which will be reported later, together with details of bacteriological findings, show progressive reduction in the concentration of bacilli and in the density of the lepromatous infiltrate.

Conclusions

Clinical improvement in such patients suffering from severe lepromatous leprosy, and consistent bacteriological improvement of the magnitude indicated, cannot be attributed to spontaneous regression. Even after this short trial period of six months, the following tentative conclusions may be drawn:

1. B 663 alone has a definite effect on lepromatous leprosy,

causing an improvement in the clinical state, a concurrent fall in the Bacterial Index, and degenerative changes in *M. leprae;*

2. This effect is enhanced by the addition of standard doses of dapsone;

3. The addition of ditophal to recommended doses of B 663 has apparently a capricious result both clinically and bacteriologically, augmenting the beneficial effect of B 663 in some patients.

4. These results indicate that the Rimino-compounds merit further trial in leprosy.

Acknowledgments

Our thanks are due to Drs. R. G. Cochrane and V. C. Barry; to Messrs. J. R. Geigy S.A. for generous supplies of their product, B 663, and for technical assistance; to Messrs. I.C.I. (Pharmaceuticals) Ltd., for the "Etisul" used in Group 3; and finally to Dr. S. E. Onwu, M.V.O., O.B.E., Director of Medical Services and Permanent Secretary, Ministry of Health, Eastern Nigeria, for permission to publish this paper.

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THE CHEMOTHERAPEUTIC ACTIVITY OF INJECTED DPT (Ciba-1906)

By F. KRADOLFER and K. SCHMID
Research Laboratories of the Pharmaceutical Department of CIBA Limited Basle

Various investigators, T. F. DAVEY (1956), J. ROSS INNES *et al.* (1957), A. M. ALONSO (1958), J. GATE *et al.* (1958), MUKHERJEE *et al.* (1958), J. M. B. GARROD (1959), have agreed that DPT exerts an optimal chemotherapeutic effect in leprosy when given in single oral doses of 1.5–3 g./day. Early observations, J. ROSS INNES *et al.* (1957), which revealed that considerable amounts of the drug can be recovered from the faeces, led to the assumption that DPT was absorbed only on a very restricted scale and that this low rate of absorption would possibly impose certain limitations on its therapeutic value. This question was subsequently re-examined in quantitative studies carried out by G. A. ELLARD (1960). Maximum oral absorption occurred in man after a single dose of 1.5 g., with no further increase in response to higher doses. However, the amount of drug absorbed could be greatly enhanced by employing a daily dose of 4.5 g. given in 3 equal fractions at spaced intervals throughout the day. These findings suggest that the restricted absorbability of the drug could partly be overcome by spacing the doses at shorter intervals.

A higher rate of excretion than after single oral doses as well as an increased rate of absorption was demonstrated to occur in animals if the dissolved drug was administered parenterally, SCHMID and TRIPOD (1959). Hence it could be assumed that in man, too, higher concentrations in the body might be attained by parenteral administration than after oral administration. In view of this possibility, a comparison of the chemotherapeutic activity of orally and parenterally administered DPT was undertaken—a comparison which should also shed some light on the effectiveness of DPT injected in suspension.

Methods

Suspension of Ciba-1906 for parenteral administration

As DPT is only very sparingly soluble in an aqueous vehicle or in oil, it was administered in the form of a 20% suspension of finely ground substance in peanut oil. If necessary, less concentrated suspensions were prepared by adding appropriate amounts of peanut oil to the stock suspension.

Chemotherapeutic investigations

As no suitable method exists so far to produce experimental infections with human leprosy bacilli, the experiments were performed on mice infected with tubercle bacilli, against which the tuberculostatic activity of DPT has been well established, R. L. MAYER *et al.* (1953), P. C. EISMAN *et al.* (1954), and E. A. KANOPKA *et al.* (1954). According to earlier findings based on experiments using tubercle bacilli, oral treatment elicits a maximum therapeutic response if Ciba-1906 is added to the diet in a concentration of 0.05%. The average daily intake of food being approximately 3 g. per mouse, the daily dose of Ciba-1906 thus works out at 70–80 mg./kg., corresponding to a total dose of 1,300–1,600 mg./kg. for the 20 days' duration of the experiment. This dose and mode of administration (standard oral treatment) constitutes the basis for comparison with the effect of injected DPT.

The chemotherapeutic effect is generally either assessed on the basis of the increased survival rate and the median survival time or measured by reference to reduction of the pulmonary lesions. The technique used here for the assessment of pulmonary lesions by measuring the lung density has been described by A. J. CROWLE (1958). The significance of the effects observed was statistically verified by the "sign test", i.e. the values for the lung density of the individual animals were randomly compared in any one group of treated mice with that of the untreated control group or with the group showing a maximum chemotherapeutic response (see Table 1).

Mice weighing 17–20 g. were infected intravenously with a suspension of *M. tuberculosis var. humanus* strain Z_3, which produces a lethal infection with a peak death rate between the 25th and 30th day. In these experiments, however, the mice were all sacrificed on the 20th day after infection, i.e. at a time when the lung density observed in untreated animals was 0.94 (standard deviation = 0.04).

DPT suspension in varied concentrations and doses was administered subcutaneously to the mice on the same day as the infection, with the exception of a special experiment in which the drug was given 9 days prior to infection.

Absorption and excretion

The amount DPT absorbed following the injection and the rate of excretion in the urine and faeces were estimated using ^{35}S labelled DPT. Details regarding the preparation of labelled DPT and the method of calculation employed have already been described by SCHMID and TRIPOD (1959). The radioactivity measured at the site of injection and in the organs or in the faeces and urine was computed as for DPT, i.e. the chemical nature of possible break-down products was studied here.

TABLE 1
Chemotherapeutic activity of single subcutaneous doses of Ciba-1906

Conc. DPT in oil suspension	*Dose mg./kg.*	*Mode of administration*	*Volume ml.*	*Time of administration*	*% Reduction in lung involvement*	*P*** (*a*)	(*b*)
5%	800	1×s.c.	0.32	Simultaneously with infection	46%	>5	5
5%	1,600	1×s.c.	0.64	Simultaneously with infection	56%	>5	>5
5%	1,600	4×400 s.c.	4×0.16	Simultaneously with infection	25%	>5	>5
20%	1,600	1×s.c.	0.16	Simultaneously with infection	80%	1	>5
—	1,300	p.o.		Beginning 1 day after infection*	70%	1	>5
5%	800	1×s.c.	0.28	9 days before infection	8%	>5	1
5%	1,600	1×s.c.	0.56	9 days before infection	46%	>5	>5
5%	1,600	4×400 s.c.	4×0.14	9 days before infection	17%	>5	1
20%	1,600	1×s.c.	0.14	9 days before infection	67%	1	>5
—	1,300	p.o.		Beginning 9 days before infection*	70%	1	>5

* and continued until 20th day after infection.
** (a) Significance of difference as compared with control group.
(b) Significance of difference as compared with group treated orally.

Results

1. *Minimum effective dose of injected DPT*

The therapeutic effect of a single dose of DPT given on the day of infection is dependent on the dose of the drug and on the volume administered (Table 1). The minimum dose producing an approximately 50% reduction in lung involvement was found to be 800 mg./kg. A dose twice this amount (1,600 mg./kg.), however, is not substantially more effective, unless given in a volume 4 times smaller, i.e. using a 20% instead of a 5% suspension. In this case a pronounced therapeutic effect is observed, an effect even exceeding that of the oral standard treatment. This difference in activity of the same dose of DPT suspension emphasises the extent to which the local absorption of the drug is dependent on the conditions of administration.

2. *Duration of activity*

If the mice are treated 9 days prior to the infection, the chemotherapeutic effect (Table 1) as compared with that of simultaneous treatment is considerably reduced only in the case of the minimum dose of 800 mg./kg. The higher dose of 1,600 mg./kg., particularly if given in the more highly concentrated suspension, still produces an effect after 9 days which compares well with that of the standard oral treatment. This fact indicates that the dose range between 800 and 1,600 mg./kg. is critical for the maintenance of a therapeutically active drug level.

3. *Parenteral absorption and drug concentration in various organs*

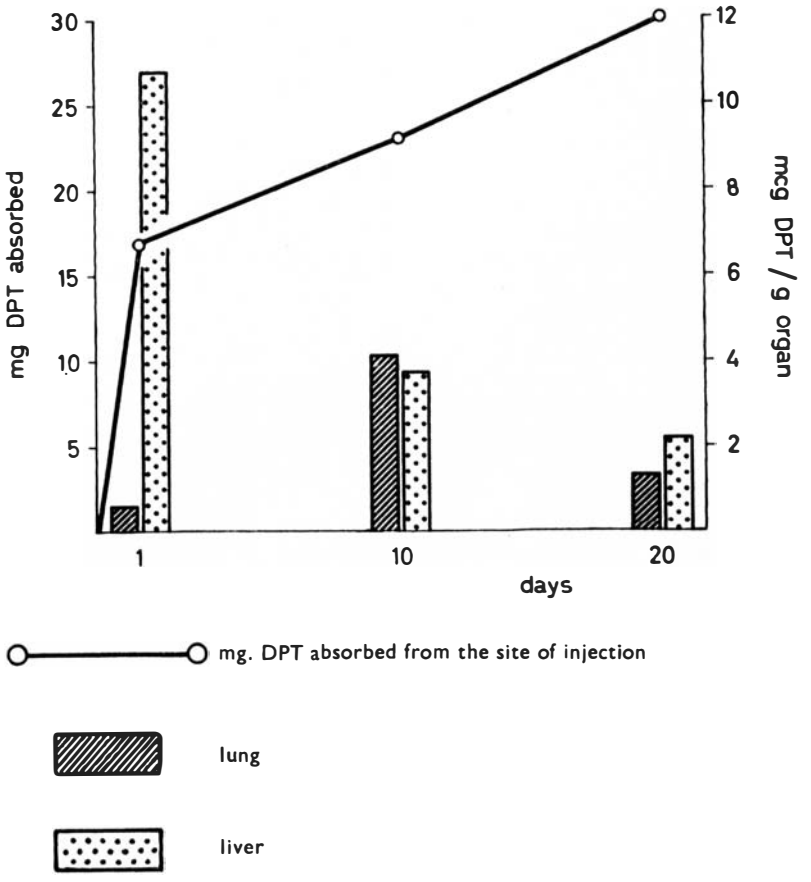
The amount of DPT (^{35}S) absorbed on the 1st day, or by the 10th and 20th day after the injection, was determined by reference to the difference between the dose administered and the amount of drug recovered at the site of injection. The resulting curve (Fig. 1) shows an initial increase followed by a rather flat slope. At the same time, it was observed that the liver accumulated a high amount of drug during the first 24 hours, whereas the lung did not participate to the same extent. Not until later, i.e. on the 10th day, when the concentration in the liver had already fallen, did the drug level in the lung attain a value similar to that of the liver. By the 20th day the concentration in both organs had decreased to approximately the same extent.

4. *Maintenance of the drug level*

The excretion of DPT and its possible metabolites was measured in terms of the amount of ^{35}S recovered in the urine and faeces of the mice, SCHMID (1961). Since losses of material are unavoidable, the amount of 9 mg. DPT which is excreted during the 1st and 2nd

FIGURE I

Drug level in lung and liver and amount of DPT absorbed after a single s.c. dose of 1,600 mg./kg.



interval of 10 days seems to be definitely superior to the amount of 7 mg. absorbed in the same period of time (Table 2). In view of this negative balance, the drug levels in the organs, after attaining an early maximum, evidently cannot be sustained for a long period. This is also borne out by the declining concentration in the organs.

5. *Minimum tuberculostatic concentration and drug level*

In experiments with tuberculous mice the target organ for the chemotherapeutic action is acknowledged to be the lung. Hence the drug level attained in this organ after a therapeutically adequate dose of DPT can be related to the minimum drug concentration

TABLE 2

Amount of DPT (^{35}S) absorbed and excreted by mice after a single subcutaneous dose of 1,600 mg./kg.

Amount of DPT recovered at site of injection expressed as % of amount injected	24 hrs. 64%	On 10th day 27%	On 20th day 6%
Total of DPT absorbed	Within first 24 hours 16 mg.	Within 10 days 23 mg.	Within 20 days 30 mg.
DPT (^{35}S) excreted* in urine and faeces	Within first day 0.4–0.6 mg.	On 10th day 0.3–0.8 mg.	On 20th day 0.6 mg.
Total excreted*		Within 10 days >9 mg.	Within 20 days >9 mg.

* Loss of some material was technically unavoidable.

required to inhibit tubercle bacilli *in vitro*. Although the data available from this work do not indicate the maximum drug levels attained, the concentration of 41 mcg./g. found in the lungs on the 10th day corresponds to a level 10–20 times higher than the (minimum) tuberculostatic concentration of Ciba-1906 *in vitro*, which, according to MAYER *et al.* (1953) is 2–5 mcg./ml. This ratio, however, may be influenced by the interference of body fluids and by metabolic changes which DPT undergoes in the host.

6. *Toxicity and local tolerability*

The possibility of injecting larger amounts of DPT, with presumably increased rates of absorption, called for comparative toxicity studies. In the case of the LD_{50} for mice, these revealed (Table 3) that no important differences exist between the injected and the oral (gavage) mode of administration.

TABLE 3

Toxicity (LD_{50}) of Ciba-1906, administered subcutaneously and orally to mice.

s.c. (mg./kg.)	*p.o. (mg./kg.)*
2,400 (±1,060)	2,400 (+900) suspended in water 4,000 (+1,200) suspended in oil

Only when subtoxic subcutaneous doses are administered (>3,000 mg./kg.) do the signs of intoxication appear earlier when a more dilute suspension (5 or 10%) is used instead of a 20% suspension (5 or 10%) is used instead of a 20% suspension—a fact which reflects the more rapid absorption from depots of larger size.

Rats and mice receiving up to 100 mg. Ciba-1906 (0.5 ml. of 20% suspension) showed an acute inflammatory reaction at the site of the depot 24 hours after the injection. Two weeks later, a non-specific, foreign-body granuloma like reaction developed, with oil droplets visible in the affected tissue.

Discussion

It is a generally agreed fact that at present there is still no adequate experimental method for the chemotherapeutic evaluation of leprostatic drugs. The present study, however, is concerned with a problem of a pharmacological nature which does not necessitate a specific infection. Thus any system enabling chemotherapeutically active concentrations of DPT to be measured either directly or indirectly in an animal may be considered suitable for the purpose in question. Both the chemotherapeutic response and analytical determination of ^{35}S labelled DPT have been used in order to investigate whether parenteral administration of Ciba-1906 can elicit a chemotherapeutic effect comparable to that obtained with oral treatment.

Earlier work by MAYER *et al.* (1953), which has been confirmed in this laboratory, showed that a 0.05% concentration of the drug in the diet was able to produce a maximum chemotherapeutic response in tuberculous mice. This dose and effect was taken by us as a basis of comparison when studying the activity of various doses of injected DPT. Not only was Ciba-1906 active by the subcutaneous route, but it also exerted a prolonged chemotherapeutic effect lasting for at least 9 days. The single dose required to achieve a maximum response under such conditions is necessarily rather high and is comparable to the total oral dose administered in a corresponding experiment of 20 days' duration.

Since the toxicity (LD_{50}) of DPT in mice is almost identical for the subcutaneous and oral routes of administration, the ratio of the dose of a depot injection to the LD_{50} is of course much smaller than in the case of continuous oral treatment, where the daily intake of DPT is only 1/20 of the total dose.

As in any other type of experiment with drugs forming parenteral depots, the volume of material injected and its colloidal or microcrystalline form are factors of major importance. The results obtained here would suggest that it is advisable to use a high concentration of the drug in order to reduce the initial absorption in favour of a more prolonged, steady degree of absorption to compensate for

the rate of excretion or destruction. The respective conditions governing the experiments on mice as described seem to approximate to a state of equilibrium only during an early period of the experiment.

The rate of absorption and excretion of DPT differs widely in various experimental animals, SCHMID and TRIPOD (1959), and it is obvious that in this respect no extrapolation to humans is possible on the basis of the present experiments. However, these experiments in mice do show that parenterally administered DPT is at least as active as the orally administered drug. It has been demonstrated earlier (MAYER, *personal communication*) that an increased oral dose did not produce a better therapeutic response in mice and that no depot effect could be obtained by oral treatment; it can therefore be assumed that also in other species, especially if oral absorption is restricted as in the case of man, J. ROSS INNES *et al.* (1957) and G. A. ELLARD (1960), the parenterally administered drug will provide higher tissue levels over a certain period of time than where the drug is given orally. The dose required for the treatment of leprosy and the duration of active drug levels achieved by the use of an appropriate concentration of DPT in a suitable vehicle must be determined clinically.

Summary

By administering DPT (Ciba-1906) parenterally in the form of a 20% suspension in oil to mice infected with tubercle bacilli, a chemotherapeutic response can be achieved which is better than the maximum effect obtained by peroral treatment. The duration of action of a single injection has been estimated by analysing the chemoprophylactic effect and the rate of absorption and excretion in relation to the concentration of ^{35}S labelled DPT measured in the liver and the lung.

Acknowledgments

The technical part of this work has been carried out by R. Schnell. For the data on toxicity and local tolerability we are indebted to Drs. J. Tripod and P. Loustalot; we are also grateful to Mr. H. Philps for revising the English version of the manuscript.

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INITIAL RESULTS OF A TRIAL OF CIBA 1906 IN DDS-INTOLERANT AND REACTION-PRONE LEPROSY CASES IN KOREA

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Patients

Heretofore unused in this institution, Ciba 1906 (diphenylthiourea) was administered to a selected group of 33 inpatients who had proved particularly difficult treatment problems, either because of reaction or DDS intolerance. These patients would fall into the category COCHRANE speaks of when he says, "Those who have had long experience in institutional work admit that there is a hard core of cases which seem to reach a certain point on the ladder of improvement, but are unable to make complete recovery".[1] Corticosteroids had been needed in controlling most of these cases during the past 18 months. The median duration since the onset of leprosy was six years. Six of these 33 patients had had the disease more than 10 years. Thirty-two of the 33 patients had the active lepromatous form of the disease.

Method

A beginning dosage of 0.5 gm. of Ciba 1906 daily was used, no attempt being made to increase this dosage until 4–6 weeks had passed with no evidence of sensitivity or reaction. The maximum dosage used in this study was 1.5 gm. daily though GARROD reports innocuousness with Ciba 1906 dosages as high as 3 and even 8 gms. daily over as long a period as 24 months.[2] Many of these patients were begun on Ciba 1906 while in the mild stage of reaction. Others were in a quiescent stage following reaction or prolonged DDS intolerance. Yet others were still on steroid therapy, usually a maintenance dosage of 5–10 mgm. prednisolone daily. In event of (1) return of reaction, (2) a definite increase in nodules, fever or neuralgia, or (3) requirement of increased dosage of prednisolone to control symptoms of reaction, Ciba 1906 was cut to 0.25 gm. per day or discontinued altogether.

Results

See Table. Each patient's response to Ciba 1906 was judged largely on clinical grounds, this being a fairly objective basis in a group of patients with such an unstable form of the disease. Those 17 who were felt to have poor response were those who had to be discontinued from use of the drug, showing the same quick flare-up

as might be elicited with reinstitution of DDS. Some of these patients had to be taken off Ciba 1906 in less than two weeks after beginning. Eleven patients, or one-third of the group were classified as having good response to Ciba 1906. A patient was considered as having a good result with lessening or disappearance of nodules, fever, neuralgia or other clinical signs of activity. Some of these cases were able to get along comfortably without corticosteroids for the first time in many weeks or months.

Special Cases

From this group of 33 patients, five cases will be described to illustrate elements of success and failure in attempted treatment with Ciba 1906.

Case No. 4: This 46 year old female with a 18 year history of lepromatous leprosy had had attempted DDS treatment for the past 4 years but was unable to take more than 0–100 mgm. per week. During November and December 1960, she was given 2 short courses of prednisolone to alleviate severe lepra reaction. In January 1961 a week of chloroquine treatment was instituted but with no relief. On January 23rd 1961, she was begun and maintained on prednisolone until July 12th, 1961.

On 28th June, 1961, the patient was begun on Ciba 1906 and two weeks later was successfully taken off corticosteroid. By the end of the fourth week of Ciba therapy, the patient had marked clearance of her nodules which had covered face and extremities and her long-standing peroneal neuralgia. Now having been on the drug for three months, the patient continues to do well. Skin smear dropped from 3+ to 1+ upon institution of Ciba 1906 therapy.

Case No. 7: This 31 year old male with a 7 year leprosy history had begun DDS three years ago, but had been unable to take the drug at all since February 1959. He began with ulnar neuralgia and recurrent nodules, especially of the face, in the fall of 1959. During the ensuing year, he received 42 injections of thiamine, approximately 30 intravenous injections of sodium salicylate, a week's course of chloroquine and 4 intraneural injections of corticosteroid. In September 1960, the patient was begun on a regular course of oral prednisolone which continued without reprieve excepting 10 days' lapse in June 1961. Ciba 1906 was begun on 1st June, 1961 and stopped after 8 weeks of 3.5 gm. weekly dosage. The patient continues to have leproma over the entire body and ulnar neuralgia unless maintained on the high dosage of 10–15 mgm. prednisolone daily. Skin smear was 3+ in January 1961, and 2+ in September 1961.

Case No. 20: This 24 year old male has not been able to take DDS since admission to our institution three years ago. In December

TABLE OF RESULTS

Case No.	Age	Sex	Type L=Lepromatous T=Tuberculoid	Years Duration	D.D.S. Duration	D.D.S. MGM Weekly Dosage	Past Lepra Reaction	Oral Cortico-Steroid Treatment	CIBA 1906 Total Dosage in grams	CIBA 1906 Stopped because of Reaction	Result
1	22	F	L	5	18 mos.	200	Mod.	3 mos.	175		Good
2	70	F	L	30	10 yrs.	4–500	Severe	1 mo.	91		Fair
3	21	F	L	5	4 yrs.	2–300	Mod.	6 wks.	145		Good
4	46	F	L	13	4 yrs.	100–0	Mod.	2 mos.	129.5		Good
5	34	F	L	11	10 yrs.	4–500	Mild		14		Good
6	32	M	L	7	2 yrs.	4–600	Mod.	1 wk.	,63		Poor
7	31	M	L	7	3 yrs.	0–200	Severe	10 mos.	47.25	X	Poor
8	24	M	L	4	6 mos.	0–700	Severe	10 mos.	14	X	Poor
9	37	M	L	8	15 mos.	0–600	Mild		66.5	X	Poor
10	30	M	L	7	12 mos.	0–600	Severe	3 mos.	24		Fair
11	24	M	L	3	3 yrs.	0	Severe	2 mos.	35		Fair
12	37	M	L	8	2½ yrs.	0–600	Severe	4 mos.	66.5		Good
13	14	M	L	4	2 yrs.	0	Mild	1 mo.	16.5		Fair
14	21	M	L	7	2¼ yrs.	300/600	Mod.	4 mos.	34		Good
15	19	M	L	5	3½ yrs.	0–300	Mod.	6 mos.	44		Poor
16	33	M	L	5	2½ yrs.	0–600	Severe	3 mos.	24.5	X	Poor
17	30	M	L	6	1 yr.	0–300	Mod.	3 mos.	14	X	Poor
18	25	M	L	16	4 yrs.	300	Severe	3 mos.	70		Good
19	37	M	L	8	1½ yrs.	0–300	Mod.		35	X	Poor
20	24	M	L	4	3 yrs.	0	Mod.	3 mos.	49		Good
21	25	M	L	10	1½ yrs.	0–600	Mod.	6 mos.	3.5	X	Poor
22	22	M	L	8	2 yrs.	0–600	Severe	12 mos.	3.5	X	Poor
23	23	M	L	7	1 yr.	0–300	Mod.	8 mos.	42		Poor
24	24	M	L	4	1½ yrs.	0–600	Mod.	3 mos.	7	X	Poor
25	22	M	L	4	2½ yrs.	0–600	Severe	6 mos.	7	X	Poor
26	24	F	L	5	5 yrs.	0–400	Severe	2 mos.	19	X	Poor
27	22	F	L	3.5	2 yrs.	0–600	Mod.	2 mos.	7	X	Poor
28	65	M	L	30.9	7 yrs.	0	Severe	4 mos.	98		Good
29	18	F	L	6	5 yrs.	400/600	Mild		7	X	Poor
30	37	M	T	12	10 yrs.	0–50			59.5	X	Poor
31	20	F	L	3	3 yrs.	0–50	Mod.		105		Good
32	21	F	L	3	15 mos.	300/600	Mod.		21		Fair
33	26	F	L	3	3 yrs.	0–600	Mod.		94.5		Good

1959, and again in February 1961, the patient was given intraneural cortisone for peroneal neuralgia with only partial relief. In April the patient flared up in reaction with widespread nodules and fever. Prednisolone was begun April 1961 and continued until 13th June, 1961. On 1st July, 1961, Ciba was begun and, aside from one week of neuralgia in mid-July, has been taken without adverse effect for the past three months.

Case No. 28: This 65 year old male with a 30 year history of leprosy had been treated for about 20 years in this institution with injections of chalmoogra oil and was found completely intolerant to DDS during the past seven years. Skin smears were negative in 1955 and 1956, 1+ in 1958 and 4+ in 1960.

The patient began with lepra reaction in June 1960, manifested by induration, erythema, fever and painful nodules. Corticosteroids begun in September 1960 brought dramatic relief and were continued for $8\frac{1}{2}$ months. Three weeks after discontinuing steroids, the patient still had some neuralgia and nodules but was begun on Ciba 1906 on 19th June, 1961. Three and one-half months later, he was continuing on Ciba 1906 with no sign of reaction.

Case No. 31: This 20 year old female with lepromatous leprosy of $3\frac{1}{2}$ years duration has responded to very small doses of DDS with leproma, headache, fever and easy onset of fatigue. On 5th July, 1961, she was begun on Ciba 1906 and has now been on the drug for over three months with no adverse effects.

Discussion

For those who showed good response to Ciba 1906 it will be necessary again to assess the efficacy of the drug after a full year of treatment. We feel that some of these will prove sensitive to the diphenylthiourea after some length of time, just as many of our diamino-diphenyl sulfone-sensitive cases do not manifest their sensitivity until after a year or more of treatment. Of course, it is often difficult to differentiate between "drug sensitivity" and the reactive phase of lepromatous leprosy unless the patient's reaction is of the erythema nodosum type. Cases No. 8, 10 and 11 had no nodules as the manifestation of their reaction, but marked neuralgia. Skin smear results following further treatment of these cases will also serve to judge the efficacy of diphenylthiourea in this DDS intolerant, reaction-prone group. A follow-up study of this same group with skin smears and the use of "Etisul" in the Ciba 1906 sensitive cases is in our plans.

Summary

Results of an initial trial of Ciba 1906 in 33 lepromatous leprosy cases either DDS-intolerant, or in a state of chronic reaction, are

reported and discussed. One-third of these patients had good response having definite clearing of signs and symptoms, thus again pointing up the important role that this drug can play in the management of a very difficult and critical problem of medical management in lepromatous leprosy.

Acknowledgment

Our thanks to Ciba Ltd. who supplied the diphenylthiourea making this study possible.

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ETIOLOGY AND TREATMENT OF PLANTAR ULCERS

"Patients must not walk on wounded feet"

W. F. ROSS, M.B.B.S., D.T.M. & H.

(*This is a report of a talk given at the Schieffelin Leprosy Research Sanatorium, Karigiri P.O.; Via Katpadi, N.A., Hospital Day* 1960.)

"Doctor my feet are killing me" is often the complaint that brings patients with planter ulcers to us. The treatment and prevention of these wounds would be made much easier if it were. As it is plantar ulcers can be prevented and cured in the great majority of cases but only by painstaking application of well understood surgical principles.

The extent of the problem

HEMERIJKX found 9.3% of 2,479 out-patients at Polambakkam, in S. India had plantar ulcers on one or both feet and the author found a similar proportion, 10% of out-patients with plantar ulcers in E. Nigeria.

If these can be accepted as indicative of the world incidence of plantar ulcers then, taking the W.H.O. estimate of total incidence of leprosy which is 10 million, we have the alarming figure of 1 million patients with wounded feet.

At Karigiri, between 25 and 30 of regular out-patients have or have had plantar ulcers and of these 50% are dependent on relatives or society for their support.

The prime difficulty in prevention and treatment of ulcers is to gain the cooperation of the patients. The treatments offered must be acceptable and effective. Many leprosy patients feel that their ulcers are an inevitable concomitant of their disease and their attitude can only be overcome by repeated and careful explanation and by the example of other patients whose feet are ulcer free as a result of treatment.

Etiology and natural history

This is necessarily a brief review and does not attempt to cover all the possible factors. Ulcers on the sole due to lepromatous leprosy *per se* are very rare, less than 1% of the total, and are not considered further.

Plantar ulcers only occur on feet which are both anaesthetic and walking. In addition it seems likely that defective circulation due to

irreversible changes in blood vessels plays some part (JOB, 1960) and it has been pointed out that fixed deformity is a very important factor in their causation (SEDDON 1960).

For practical purposes these ulcers may be divided into two groups:

I. First ulcers on virgin feet.

II. Recurrent ulcers on previously damaged feet.

Essentially the etiology of both is the same; but, as is well-known, once a patient has had an ulcer it is extremely difficult, but not impossible, to prevent a recurrence.

I. THE FIRST ULCER

(a) *Casual Trauma.* Some ulcers are caused by casual trauma. By this is meant cuts, burns, thorn wounds, surface friction blisters and injuries due to badly fitting shoes or badly made shoes, e.g. nails sticking into sole. The natural history of such an ulcer is a break in the skin, often quite minor, unnoticed by the patient who continues to walk. The wound becomes infected. There is local oedema and regional lymphadenopathy and the wound, subject to the trauma of walking fails to heal. Recently, I had such a wound myself. I was well aware of it but continued to walk, partly out of curiosity. In 3 weeks it did not heal despite daily dressing and at the end of the time I had painful glands in the groin and a very sore foot. Then I was confined to bed for three days by fever, and the wound healed.

"Patient must not walk on wounded feet".

(b) *Plantar Warts.* Occasionally, ulcers occur under plantar warts and they are sometimes seen after unskilled cutting for corns or careless removal of callosities.

(c) *Cracks.* Another relatively uncommon cause of ulceration is the infected crack. Many barefooted people have dry feet and when the hardening effect of repeated immersion in water followed by rapid drying in the hot sun is added to anhydrosis and skin atrophy due to nerve involvement, then the soles become very dry and hard indeed. Such soles are prone to cracks. Deep cracks may extend to the subcutis and provide an opening for bacilli and the beginning of an ulcer. These cracks are commonly found at the lateral margins of the heel and at the flexor creases in the forefoot. (Figure 1.) Tiny hairline cracks are also found on the weight bearing surfaces, particularly in patients who wear hard leather chappals whose feet are polished like patent leather. The cracks may be alleviated by regular oiling of the feet and prevented from becoming deep by means of rigid sole footwear.

(d) *Subcutaneous Necrosis.* We find that these three factors, casual trauma, plantar warts, and infected cracks account for only a small

FIG. 1. TO SHOW THE COMMON SITES OF DEEP CRACKS IN ANAESTHETIC FEET.

proportion of sole wounds. These three show, first a break in the skin, then bacterial invasion and then a septic superficial ulcer which will, unless localised, cause spreading inflammation. But the true and common plantar ulcer begins as a deep necrosis, often at its first appearance penetrating from the skin to plantar fascia or tendon sheath.

(1) *The pre-ulcer.* The first stage of such an ulcer is an aseptic inflammation of subcutaneous tissue which manifests itself in three ways.

(i) Tenderness over the affected zone. Despite the fact, that all these ulcers occur in feet with some sensory deficiency, deep pressure sensation at the metatarsel heads is rarely lost and deep tenderness is a reliable early sign of inflammation (PRICE, 1959).

(ii) Swelling of the tissues and slight spreading of the toes. There is localised oedema resulting in the toes adjacent to the affected zone being forced apart.

(iii) Often there is visible in the subcutis a small, uninfected haematoma. Ulcers are rarely seen at this stage in outpatient work but they can be picked up at a resident institution, particularly where patients' feet are regularly examined. If a patient with tenderness, swelling and subcuticular haematoma on the foot is put to

bed for a few days, the whole thing subsides. If he continues to walk the second stage of ulceration ensues. This is necrosis of the zone of inflammation.

(2) *Subcutaneous Necrosis.* In the first place this necrosis is aseptic and even at this stage if the patient is put to bed, healing will take place.

(3) *The Open Ulcer.* The third stage is rupture of the haematoma following which infection supervenes. The necrotic tissue is liquefied and in a few days the typical punched-out deep plantar wound penetrating from skin to underlying fascia or tendon sheath develops. These ulcers essentially develop from within outwards. Skin break and infection are late complications.

Etiology

How can their development be accounted for? It should be noted that these ulcers occur only on feet that are both anaesthetic and walking. There are two possible explanations.

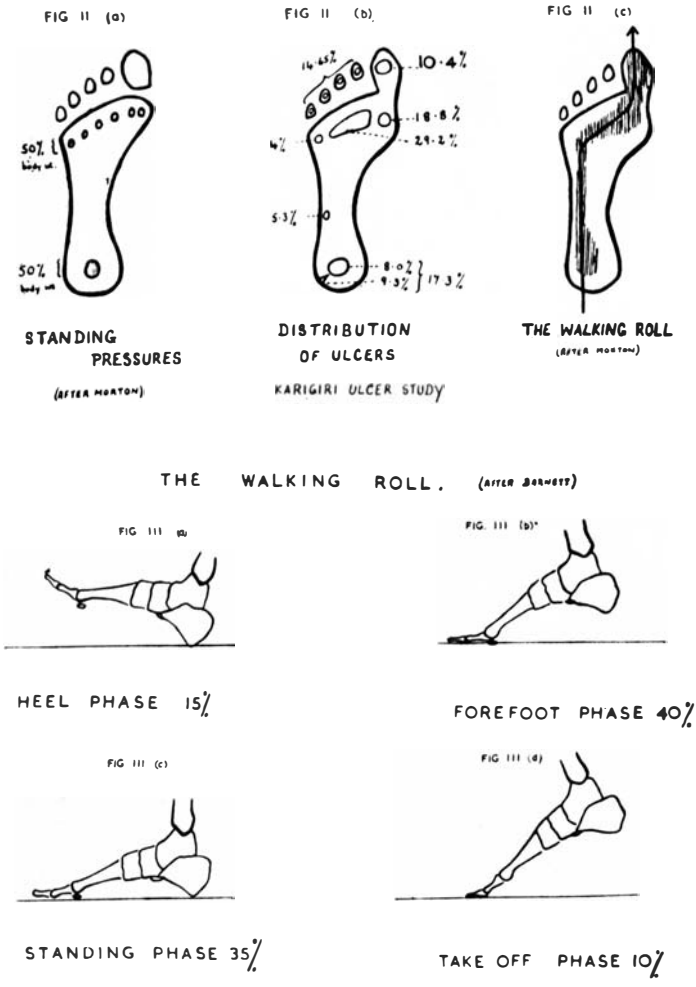
First, that the ulcer is due to pressure leading to ischaemia and localised gangrene of tissue while weight-bearing on an anaesthetic foot. If this was so, we would expect the distribution of wounds to correspond to the distribution of weight in the standing foot, for during walking weight is only borne on any one part of each foot for one eighth of a second or less which is nothing like enough time to give ischaemia sufficient lead to gangrene. But the distribution of ulcers does not correspond to the distribution of weight on the standing foot.

The second possibility is that friction forces set up within the foot (Figure 2a) during walking lead to mechanical damage to the tissues and eventually necrosis and ulceration.

If this is the case we would expect the distribution of ulcers to correspond to the distribution of friction forces in the foot whilst walking. It will be seen from the figures that this is in fact what has been found (Figures 2b and 2c).

The relationship between forces acting on the foot during walking was hinted at by BRAND and FRITSCHI in 1957 and clearly demonstrated by PRICE in Nigeria in 1958. Observations made at Karigiri agree with Price's finding and although our demonstrations at Karigiri show that most ulcers occur not under but in front of the metatarsel heads.

(Figure 3.) This confirms the theory of causation put forward by PRICE. BARNETT (1956) divides the period during which the foot is partially or wholly in contact with the ground in walking, about three-quarters of a second for each step, into 5 phases, which together constitute the walking roll.



1. The roll begins with the impact of the posterior lateral aspect of the heel on the ground quickly followed by the complete heel. This phase occupies 15 to 20% of the cycle (Figure 3a).

2. It is followed by the standing phase in which the heel, outer side of sole and the metatarsel head are in contact with the ground. This phase couples 30 to 35% of the total roll and during it the distribution of pressure is much the same as during standing.

3. During the third or metatarsal heel phase which occupies 10% of the roll, the weight is borne only on the metatarsal heads, the heel rising from the ground and extension taking place at the metatarse phalangeal (m.p.) phase is occasionally absent as a separate phase.

4. The fourth or fore-foot phase follows. Thrust is borne on the metatarsal heads and the toes, the hallux and 2nd toe predominating. The heel continues to rise and further extension occurs at the m.p. joints. The metatarsal heads will rotate through as much as 40 degrees and as the skin is fixed to the ground this rotation is absorbed in the tissues between skin and m.p. joints. It is during this phase that maximum forward thrust occurs, resulting in compression forces behind the metacarpal heads, and shearing forces beneath them and tension in front (Figure 3c).

5. The final step-off phase occupies 3 to 10% of the roll. Thrust is borne entirely by the toes, the main part of it by the hallux (Figure 3d).

The forces just described act at every step in normal feet as well as in anaesthetic feet. In normal feet, no change is done. In anaesthetic feet, proprioceptive reflexes which normally adjust the pressure put on the foot to the minimum necessary to prevent slipping during walking are out of action. The result is that at each and every step maximum force is exerted on the foot particularly at heel impact and forefoot thrust and the tissues are damaged through sheer overwork. It will be seen that, if as is believed, most plantar ulcers are due to forces acting within the foot and that the most damaging ones act on heel impact and m.p. extension during the thrust of forefoot and metatarsal phase, then a high proportion of these ulcers can be prevented by cushioning heel impact and by reducing or eliminating rotation at the m.p. joints. This can be done by means of rigid sole shoes with microcellular rubber insoles, which will be described in a further section.

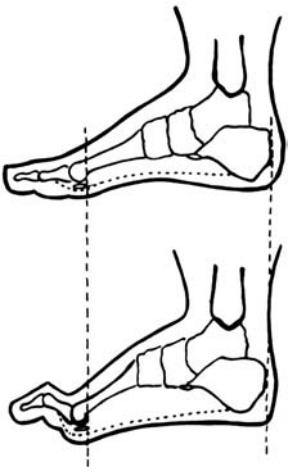
There is another factor in the etiology of these wounds which should be mentioned because of its bearing on prevention and treatment, i.e. the effect of paralysis.

1. Drop foot due to various degree of lateral popliteal paralysis. The patient walks with a high stepping gait and the foot slaps on to the ground with the whole lateral border. This frequently results in ulceration at the head and the base of the 5th metatarsal.

2. Claw toes due to intrinsic paralysis. The effect of clawing of the toes is threefold. (i) Tissues under the metatarsal heads are put on the stretch. (ii) The toes no longer play their part in walking and all take-off thrust is borne by the metatarsal heads, BARNETT (1956).

3. The arch is raised and the metatarsal heads are relatively lowered, HICKS (1954) (Figure 4). If this process proceeds equally in all five toes then no damage may be done but if one toe is a little more clawed than its neighbour then the associated metacarpal head is pushed down below the adjacent heads and bears an increased proportion of the take-off thrust. The treatment for such

Fig. IV



CLAW TOES, WINDLASS EFFECT

ARCH RAISED & FOOT SHORTENED

AFTER HICKS.

protruding metatarsal heads is not to trim them, as some recommend, but to correct the clawing and restore the metatarsal head to its normal position in line with its fellows, BRAND and FRITSCHI (1957).

II. RECURRENT ULCERS ON PREVIOUSLY DAMAGED FEET

In addition to anaesthesia the foot with healed ulceration may display the following defects.

(a) Scarring and loss of friction reducing mechanism. (b) Necrosis blister. (c) Fixed deformity (SEDDON, 1960). (d) Discreet cysts of purulent material.

(a) *Scarring and loss of friction reducing mechanisms.* Scar tissues being rigid and having poor blood supply, is much less able to withstand the stress forces set up in the heel and forefoot during walking than normal tissue. If in addition to scarring the smooth cartilaginous surface of the normal metatarsal head has been destroyed, the already abnormal tissues are literally ground between the rough metatarsal head and the walking surface. It is not surprising that such feet will re-ulcerate after as little as 15 minutes of walking. Callosities and hyperkeratotic scars are common findings. These are often as hard as stones and must be removed, or fresh wounds will result.

(b) *Necrosis blisters.* This is a subcuticular collection of tissue fluid with black necrotic debris floating in it which is usually sterile. It usually appears as a blister at the margin of the foot where the thick volar skin meets the thin dorsal skin. These blisters are commonly attributed to burns. They are not burns. The fluid has tracked under the plantar skin from a deep-seated sterile necrosis at the site of a previous ulcer. If the blister is left untouched, and the patient put to bed, it will dry up without further trouble.

If the patient continues to walk, the blister ruptures, infection supervenes and an infected wound results.

(c) *Fixed deformity.* In patients with sciatic nerve lesions SEDDON found that "loss of sensibility of the sole is far less important than the fixed deformity" in the causation of persistent ulceration.

Fixed deformation or deformities do not appear to play such an important part in the causation of ulceration in leprosy patients, but SEDDON's statement serves to underline the difficulties that ensue when secondary fixed deformities are allowed to develop, and the extreme importance of detecting the pre-ulcer and thus preventing the bone and joint infection that so commonly leads to fixed deformity.

(d) *Intermetacarpal abscess.* It has been pointed out, KULONSKI and OERIMAN (1936), that small cysts containing pathogenic organisms are commonly present in anaesthetic feet which have at one time or another had plantar ulcers. These small abscesses may at any time flare up and give acute septic inflammation in the tissues of the foot. The nidus of infection may be in the bone, particularly metacarpals or calcaneum, in cartilage or tendon or in subcutaneous tissue. It may contain a small foreign material such as a thorn or a piece of dressing or it may simply contain purulent material and bacteria. The factors which cause such a cyst to become active after as much as 9 years, as was the case of one patient known to me, are not known but the clinical picture is clear. The patient presents a hot, swollen, painful foot, with lymphadenitis. The treatment is strict bed rest, drainage of the abscess if it can be located and administration of antibiotics.

Treatment

1. *Curative.* The principles of treatment of infected wounds have been known for a very long time; probably the greatest exponents in recent years have been WINNET ORR and TRUETTA and the following notes are based on TRUETTA's classic work, "The principles and practice of War surgery", 1944. The treatment advocated may be summarised as follows:

1. Clean the wound.
2. Excise dead tissues.

3. Allow free drainage.
4. Immobilize the part.
5. Prevent secondary infection.
6. Stop reception of the trauma causing the wound.

"Patients must not walk on Wounded Feet".

Let us see how these principles apply to three different types of ulcers.

1. THE VIOLENTLY AFFECTED WOUND

These are found in association with hot swollen feet, with inguinal adenitis and with copious discharge from the wound.

1. *Clean the wound.* This may best be done with warm water and soap.

2. *Excise dead tissue.* Anything obviously dead should be cut away, the object being to remove all slough, without drawing blood. In addition the fibrous scars often seen at the edge of these wounds should be cut away to allow the epithelium to grow.

3. *Allow free drainage.* Drainage is usually adequate after the dead tissue has been excised, but if not then further incisions and, if necessary, excisions of healthy tissue, must be made until the wound is in no danger of becoming an abscess.

4. *Immobilize the part.* These limbs should be encased in a light non-weight bearing plaster of paris cast (p.o.p.). They are not suitable for ambulant treatment with p.o.p. The excised wound should be packed, with sterile vaseline gauze or gauze soaked in flavin and paraffin and the p.o.p. applied. In the case of really stinking wounds, filling the wound with 2% soap solution and then packing with gauze also soaked in soap solution materially reduces the smell.

5. *Prevent cross infection.* The commonest vehicles of cross-infection are doctors, nurses, orderlies and the patient himself. All these agents may be prevented from adding infection to the wound by encasing it in plaster of paris cast.

6. *Stop repeating the trauma.* The p.o.p. cast obviously entirely cuts out the walking roll which is the underlying cause of most of these ulcers.

Such a regime will heal any ulcer, no matter how big or badly infected. If the wound is really purulent, after a few days, discharge will begin to show through the plaster. Provided that the patient's condition is satisfactory, i.e. his temperature is normal and lymph-adenitis subsiding, the smell may be ignored. The smell from a healing purulent ulcer is quite characteristic and may be confidently described as a "laudable odour". If the discharge has not ceased and

the smell subsided in two to three weeks after the application of the plaster, then the plaster should be removed under aseptic conditions and the wound re-examined. It will usually be found either the drainage is inadequate or that a previously undetected sequestrum is present.

2. THE CLEAN DRY ULCER

These ulcers show no oedema of the foot, no inguinal adenitis and little or no discharge. They may be treated along the same lines but bed rest is not necessary and they can be sent home in a weight-bearing plaster of paris cast, or "Karigiri Boot" (Figure 6). See Appendix 1 for details of the "Karigiri Boot". We find that 6 weeks is a reasonable time to expect p.o.p. casts to remain intact. Proprietary brands of p.o.p. will last longer and some patients, particularly in wet weather, will break up any type of plaster in much less than 6 weeks. If finances allow, glassona, which is a plastic type of cast developed by Messrs. Smith & Nephew, may be used. It is very tough and water repellent, and will last indefinitely. The "Karigiri Boots" will last 8–12 weeks. We find that these clean, dry ulcers heal at the rate of approximately 0.25 cms. per week. This is about half the rate of growth of epithelium under optimum conditions. Unless the patient is prepared to go home to strict bed rest we advise this type of treatment for practically all dry plantar ulcers, however small.

3. THE MILDLY INFECTED ULCERS

These patients show minimal discharge slight oedema of the foot and little or no inguinal adenopathy. They are not suitable for immediate application of weight-bearing p.o.p. or "Karigiri Boot". We admit these patients to the ulcer ward for treatment, designed to convert these ulcers into dry, relatively uninfected ones.

1. Cleanse the wound with daily soap and water soaks.
2. Excise dead tissue.
3. Provide drainage.

4. IMMOBILISE THE PART

These patients are put on strict bed rest. "Patients must not walk on wounded feet." And after a few days of repeated soaks they are ready for application of weight-bearing p.o.p. or "Karigiri Boot" and discharge.

5. THE INFECTED CRACK

The large majority of these cracks will heal satisfactorily in 2 to 4 weeks if the edges are excised, the wound cleaned and then immobilised by strapping a wooden rocker with a felt insole on to the foot by means of elastoplast. This method of immobilisation will

prevent ulcers from becoming worse but is not a reliable method of treatment except for infected cracks as mentioned above. If a sinus is associated with a crack, then excision to provide free drainage and immobilisation in a weight-bearing p.o.p. cast is essential. There are three further adjuncts to treatment which should be mentioned.

(1) *Antibiotics.* These are not necessary and their use in in-patient treatment is not recommended because of the chronicity of most of these ulcers and the danger of populating the hospital premises, staff and patients with resistant organisms. If bed space is not available for preparing the mildly infected type of ulcer for p.o.p., then careful cleansing of the wound, excision of dead tissue in out-patients followed by application of felt and a rocker and the administration of 4 cc. of a long-acting penicillin is recommended as a practical alternative.

These patients should be asked to report after one week. It may be that careful use of antibiotics after sensitivity testing would reduce the period of hospitalisation needed to prepare infected wounds for weight-bearing casts, but this has yet to be demonstrated.

(2) *Preventative surgery.* Claw toes and foot drop secondary to paralysis should be corrected preferably by tendon transfer, BRAND and FRITSCHI (1957). Toes which are twisted and rigid, should be removed. The only bone cutting operation which commends itself is the removal of the spur of bone from the underside of the calconeum which is commonly present following an ulcer on the heel, DREISBACH. The utmost conservatism should be the rule when considering surgery of the metatarsals. If sequestration occurs, remove the sequestrum but normal metatarsal heads should never be removed.

(3) *Ascorbic acid.* The work of the RAO *et al.* (1956) has shown that the majority of people in South India are deficient in ascorbic acid. The importance of this vitamin in the healing of wounds has been demonstrated many times and although no controlled study has yet been carried out in the healing of ulcers in leprosy patients, it is recommended that all ulcer patients should receive at least 300 mgm. of ascorbic acid daily whilst under treatment, and it would probably be wise to continue to administer the vitamin in lower dosage for a prolonged period.

APPENDIX 1. The "Karigiri Boot" (Figure 6). This boot has been developed from the shoe described by Brand in an addendum to Chapter XXII of "Leprosy in Theory and Practice", Cochrane, R.G., 1959.

It is cheap, costing approximately 5/–, effective, acceptable to the patients and can be applied to outpatients who have to go home the same day. It may be applied to all cases suitable for the application of weight-bearing p.o.p. casts.

Appendix 2

Pre-vulcanised rubber latex may be obtained from: The Dunlop Rubber Co., Chemical Products Division, Erdington, Birmingham. Please mention the purpose for which the latex is needed as Dunlops are making a special mix for me. Revertex Ltd., 51/55, Strand, W.C.2. Ask for Mr. Revultex. Rubber Latex Ltd., Harling Road, Wythanshaw, Manchester 22.

Karigiri Boot

Further experience has shown that a wooden clog may be used to provide the rigid sole for the Karigiri Boot. This can be either made locally or obtained from: Snaith Clog Manufacturing Co., Snaith, Yorkshire. Old nylon stockings are an effective substitute for the cotton socks originally described, and a similar stocking drawn over the outside gives a neat finish to the boot.

FIG V THE "SHUFFLE BOARD"

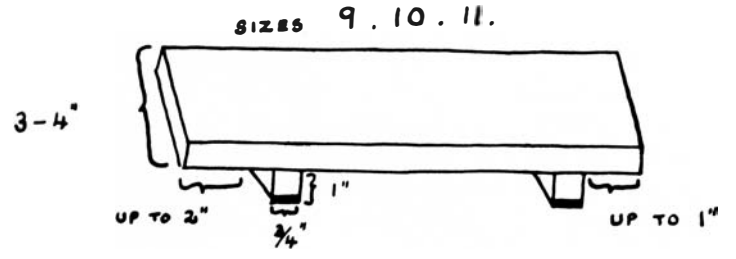
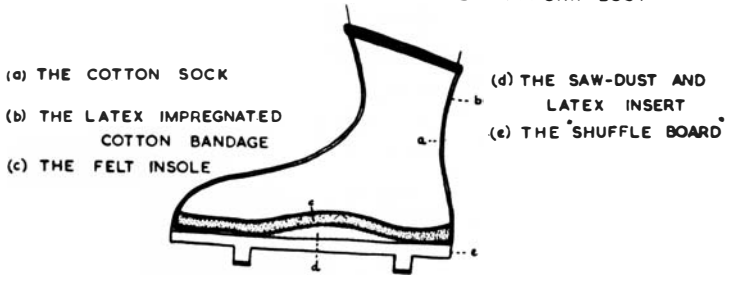


FIG. VI LONGITUDINAL SECTION OF THE "KARIGIRI BOOT"



"KARIGIRI BOOT"

The Boot is made as follows:

1. A cheap cotton sock of suitable length, or stockinette, is soaked in prevulcanised rubber latex. If the prevulcanised cannot be obtained then crude latex is almost as good but takes rather longer to dry. Both these substances can only be obtained in India under licence.

2. A piece of saddler's felt is cut sufficiently large to cover the whole sole of the foot and, after the application of a piece of dry gauze to the ulcer, the felt is applied to the sole (any cheap felt is suitable), provided that it is clean and approximately $\frac{1}{2}$ inch thick.

3. The latex impregnated sock is then drawn on to the foot over the felt, so as to hold the felt in place. The felt being inside the sock.

4. A handful of clean dry sawdust is then mixed with the latex to form a stiff paste.

5. A "Shuffle Board" is applied to the outside of the sock and the interstices between the board and the sock packed with the latex sawdust paste.

6. The whole is then bound firmly together by means of an open weave cotton bandage also soaked in the latex. The procedure is similar to the application of a skin tight plaster of paris cast to the foot and ankle, and the precautions should be observed. It is important to keep the foot at right angle to the leg during the application of the bandage and until the latex is reasonably dry, and to rub the boot to expel all the air from between the bandages during their application.

The boot may extend only to the ankle, or it may easily be extended up the leg to the knee. Both the cotton sock, or stockinette, and the bandages must be thoroughly soaked in the latex so that every thread is coated with rubber, but they should not be dripping wet. The easiest way to achieve this is to pour latex into an open dish to a depth of about one inch and then kneed the latex into the sock as a baker kneads water into his dough. The bandage should be rolled up simultaneously in the latex, again kneading the latex into the bandages as it is rolled. It is not sufficient to stand or even squeeze the rolled up bandage in the latex. Additional amounts of latex may be added to the dish as necessary. Two 3 in. $\times$ 108 in. bandages are sufficient for a boot of average size, more will be for large feet or the long boot.

THE "SHUFFLE BOARD"

This is a plain piece of board, box boarding is quite suitable, 3–4 inches broad and long enough to extend beyond the heel and toes, sizes 9, 10 and 11 inches will cover the majority of patients. Fixed to the under surface of the board are two wooden bars, each

3 inches broad and 3 inches deep, shod with narrow strips of tyre-sole rubber. The rear bar should be 1 inch from the back and the front bar approx. 1½ inches from the front.

The best position for the enterior bar, its optimal depth and its relationship to the metatarsal heads is still not finally settled. If the bar is at or behind the metatarsal heads then the foot can roll around the bar and at or behind the metatarsal heads and the gait will simulate the normal (Figure 7).

The main advantage of bringing the bar as far forward as the metatarsal heads is that a low bar is then sufficient to give an adequate take-off angle, whereas if the bar is near the centre of the board a very high bar is needed if an adequate angle is to be achieved (Figures 7 and 8). A high bar is unsightly and makes the gait unbalanced and unstable. It will be recalled from the section on etiology of ulcers that the normal take-off angle at the metatarsal heads may be up to 40 degrees, but anything over 30 degrees will enable the patient to walk in reasonable comfort and at a good pace, in these boots. If a single bar is used which is too low or not forward enough, then the foot is forced to pivot about the anterior end of the board and this result is excessive strain on the instep and probably on the

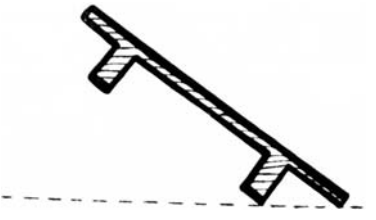


FIG. VII. DIAGRAM TO SHOW THE TAKE OFF ANGLE WITH A ONE INCH BAR ONE AND HALF INCHES FROM THE ANTERIOR AND OF THE BOARD.

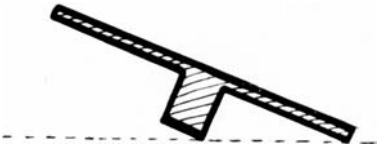


FIG. VIII DIAGRAM TO SHOW THE TAKE OF ANGLE WITH A TWO INCH BAR FIVE INCHES FROM THE ANTERIOR END OF THE BOARD.

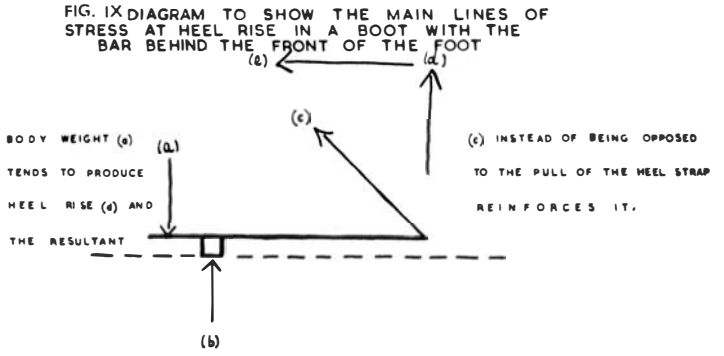


FIG. IX DIAGRAM TO SHOW THE MAIN LINES OF STRESS AT HEEL RISE IN A BOOT WITH THE BAR BEHIND THE FRONT OF THE FOOT

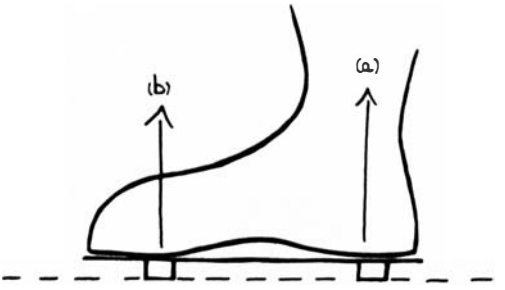


FIG. X DIAGRAM TO SHOW THE SHUFFLE GAIT HEEL (a) AND TOES (b) RISE ALMOST SIMULTANEOUSLY. NO ATTEMPT IS MADE TO LIFT THE FOOT UNTIL TOTAL BODY WEIGHT IS TRANSFERED TO THE OTHER FOOT.

metatarsal heads also (Figure 9). Similarly if the anterior bar is placed in front of the fore then in the attempt to walk normally very great stress is thrown on to the heel-strap (Figure 9). Some patients persist in the attempt and succeed in cultivating a normal looking gait but at the expense of very much strain in the portion of the boot which keeps the heel in place on the shuffle board. Other patients adopt a shuffle walk in which no attempt is made to lift the foot until total body weight is transmitted to the other leg (Figure 10). The foot is lifted almost vertically upwards at take off, carried it forward, more or less parallel to the ground and then placed squarely on the ground at the beginning of the next phase of gait.

This gait probably completely eliminates thrusts at the metatarsal heads but it is ungainly and tiring. Our patients have done uniformly well in these boots whatever type of gait they have adopted.

Acknowledgements

My grateful thanks for help and guidance to my teachers Dr. Paul Brand and Dr. E. W. Price.

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STUDIES ON THE STRUCTURE AND FUNCTIONS OF THE PAPILLARY RIDGES OF THE DIGITAL SKIN IN LEPROSY

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It is generally assumed that there are different sensory modalities associated with the specific sensory receptors of skin. Nerve endings of the fibrillary structures are found in hairy and non-hairy skin in relation to certain cells of the basal cell layer of the epidermis where the nerve endings and the cell constitute as sensory receptors. Touch sensibility of hairy and hairless skin are of different orders. In hairy skin it is arranged into a spot pattern and in non-hairy skin it is evenly spread over the surface papillary ridges.

The histological structure of the leprosy lesion in the skin is very distinctive. In lepromatous leprosy, the epidermis is thinned. The cell layers are flattened and slightly irregular. The papillary ridges are completely flattened and compressed. There is a free sub-epidermal zone where cellular infiltrations are characteristically absent. In tuberculoid leprosy, the epidermis is thinned in the particular area where the lesion starts. In advanced tuberculoid leprosy, the papillary ridges are completely flattened and irregular. The sub-epidermal zone in contrast to lepromatous leprosy, does not appear as a clear zone but is invaded by the inflammatory infiltrate reaching up to the epidermis. This clearly shows that in leprosy irrespective of type the structural damage to the epidermis is more. The purpose of this investigation is to study the changes that occur to the papillary ridges in leprosy and to determine the relation of those changes to alterations of cutaneous sensibility found in leprosy. Digital skins were primarily chosen for the investigation as the touch sensibility in this part of the skin is evenly spread over the papillary ridges in normal individuals.

Materials and Methods

Thirty pieces of skin were taken from the distal pads of the fingers from thirty patients showing typical lesions of leprosy. 20 were taken from lepromatous leprosy and 10 from tuberculoid

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cases. There were no visible lesions anywhere on the finger pads. Biopsies were also taken from lesions of each patient to confirm the type of lesion histologically. Tissues were fixed in 10% neutral formalin and frozen sections were taken at 20 micron thickness and stained by the method described by BALASUBRAMANYAM, JAYARAJ and GASS (1954) for nerve fibres. 20 sections were taken from each specimen for this study. Remaining tissues were processed for paraffin sections. Sections were stained with haematoxyline and eosin and for acid-fast bacilli by the method described by JAYARAJ (1955). 5 specimens were taken from the distal pad of fingers of normal individuals as control.

Observations on Cutaneous Sensibility

Tactile sensibility was observed with the tip of a fine feather on the distal pad of the fingers before biopsies were taken. Stimuli were applied with lighter touch to heavier touch and with fine pin points.

It was found that in early lepromatous leprosy the finger pads responded to light touch and in advanced lepromatous leprosy the site was anaesthetic to light touch but responded to heavy touch. Occasionally the finger pads were found to be anaesthetic to heavy touch but responded to fine pin pricks.

In tuberculoid leprosy the finger pads did not respond to heavy touch with the feather but responded to pin pricks. Occasionally they were anaesthetic to pin pricks also.

Results

Changes in the epithelial pattern in relation to nerve endings in papillary ridges in lepromatous leprosy: The epithelium is flattened leaving the surface of the papillary ridges in limited length in the corium. The ridges are prominently seen even though the epithelium is flattened. The ridge is embedded in loose connective tissue and its deep surface is in contact with the ascending nerve fibre of the corium. The ascending fibre is seen damaged by way of ballooning. There are numerous neural fragments seen embedded in the papillary ridges. The sweat passages are seen in the middle of some of the papillary ridges. There is no marked difference in histology between the early lesion and advanced lesion excepting that the papillary ridges are found to vary in length. The ridges project more in length in the corium in early lepromatous leprosy and less in advanced lepromatous leprosy.

Changes in Tuberculoid Leprosy

The thickness of the epithelium is reduced. In some places, the epithelium is flattened and there are no papillary ridges seen. The subepithelial part of the corium shows no nerve fibres. Very

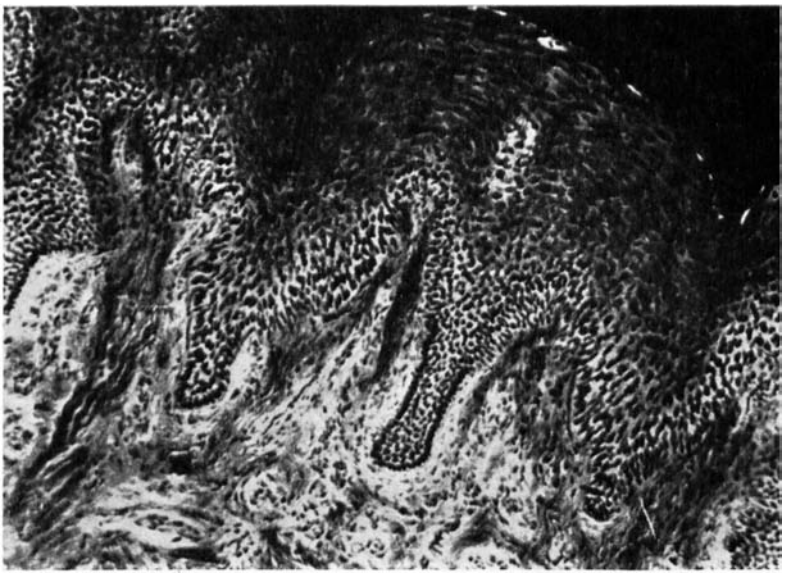

FIG. 1. Transverse section of the digital skin showing the papillary ridges and the sub-epidermal nerve plexus underneath the ridges. Distal pad of the middle finger, Male, 30 years—Manual worker x 100.

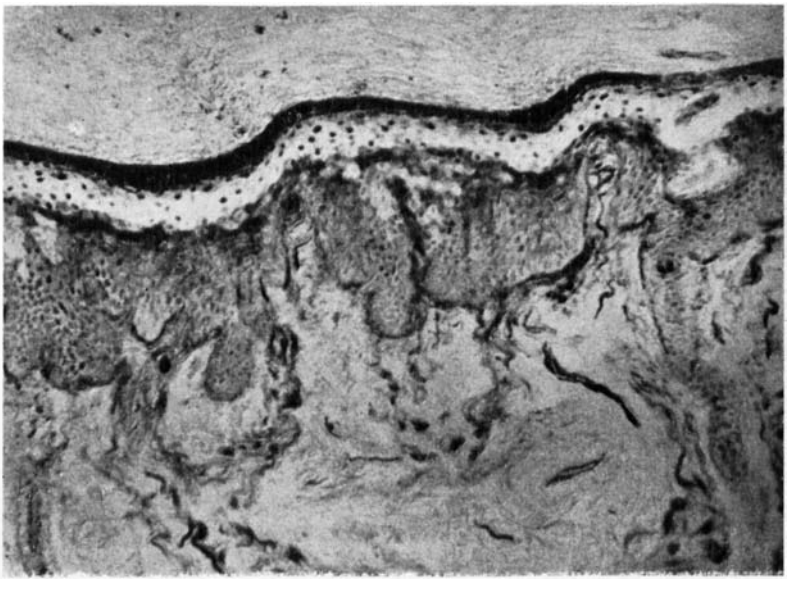

FIG. 2. Transverse section of the digital skin showing flattened epithelium with limited papillary ridges descending less deeply into the corium and the sub-epidermal nerve plexus underneath the ridges. Distal pad of the ring finger, male, 25 years. Lepromatous x 100.

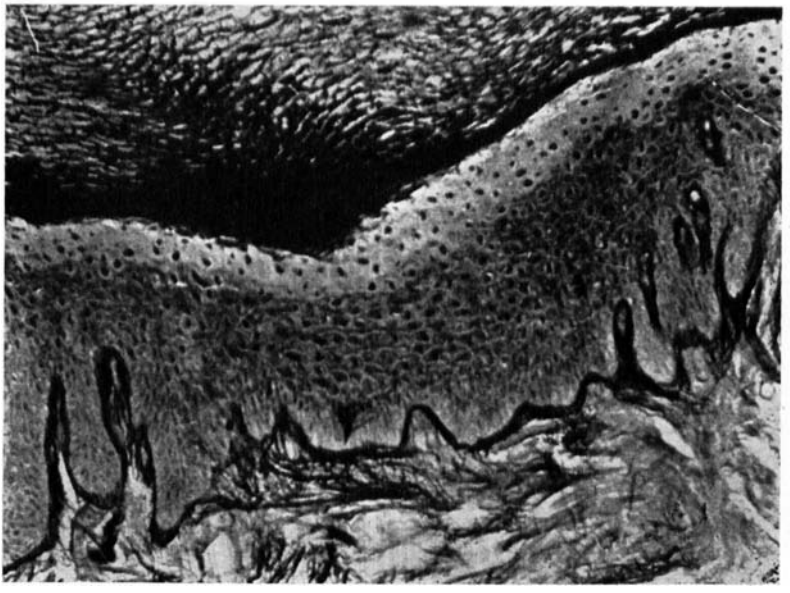

FIG. 3. Transverse section of the digital skin showing the epithelium with flattened papillary ridges and the sub-epidermal area completely invaded by connective tissue elements. Distal pad of the middle finger, male, 27 years, Tuberculoid x 100.

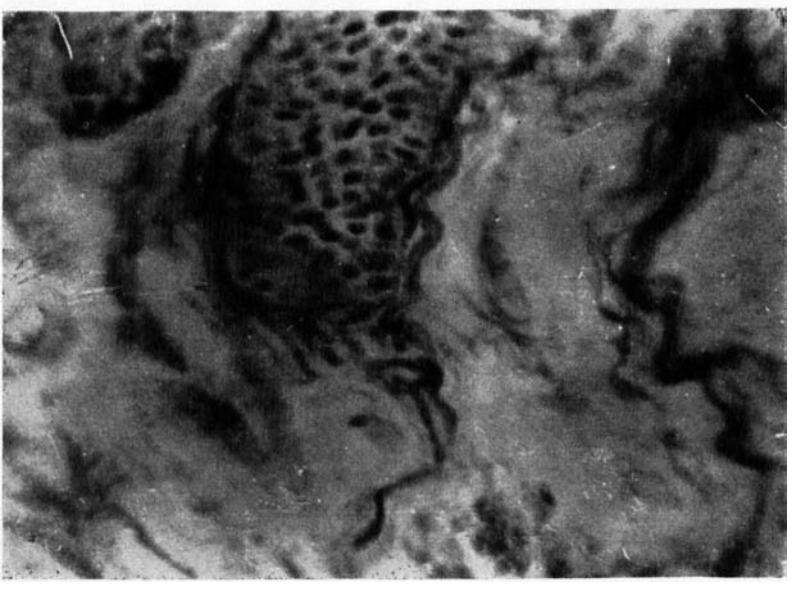

FIG. 4. Transverse section of the digital skin showing the papillary ridge in contact with extensive nerve plexus. Distal pad of the ring finger, male, 25 years. Lepromatous x 400.

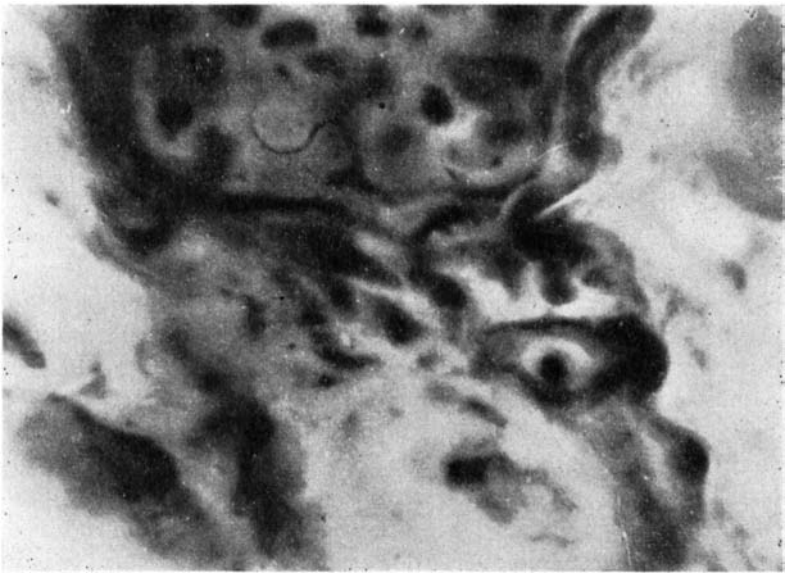

FIG. 5. Higher magnification of fig: 4. showing the epidermal nerve ending on the papillary ridge x 900.

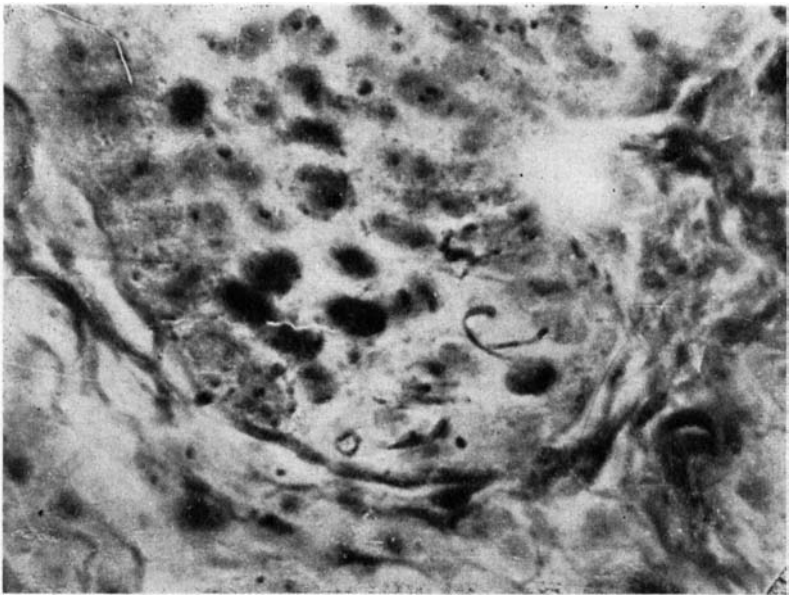

FIG. 6. Transverse section of the digital skin showing the neural fragments situated in the papillary ridge. Distal pad of the middle finger, male, 25 years. Lepromatous x 900.

occasionally fine nerve fibres are seen coursing towards the epithelium. Nerve endings in relation to any part of the epithelium is absent. However there are some fine nerve fibres seen coursing towards the Meissner corpuscle.

Discussion

The stratum corneum of the digital skin is much thicker than that of the hairy skin. Yet the finger tip performs the function of an efficient tactile sense organ with high sensibility and discrimination. CAUNA (1954) observed that the papillary ridges contain separate receptors for tactile acuity and discrimination, and the Meissner corpuscle is a selective receptor for pressure that coincides with the axis of the corpuscle and is primarily concerned with tactile discrimination. He has beautifully demonstrated a rubber model of the papillary ridges showing the function of the intermediate ridge and the Meissner corpuscle. The intermediate ridge is embedded in loose connective tissue and is not attached to the corium. It is in contact with an extensive nerve plexus with epidermal nerve endings. CAUNA has shown that the intermediate ridge follows the movements of the papillary ridge acting as a magnifying lever mechanism for transmission of touch stimuli to the underlying receptors. It can be equally stimulated through different surface areas of the papillary ridge and is primarily concerned with tactile acuity. Even though the epithelium is flattened in lepromatous leprosy the intermediate papillary ridges in the digital skin are seen distinctly and the ridges are definitely in contact with extensive sub-epidermal nerve plexus.

These findings on the basis of histological and functional considerations justify that the papillary ridges in lepromatous leprosy continue to act as part of essential tactile sense organ. JAYARAJ and CHAUDHURY (1961) have shown that the Meissner corpuscles in lepromatous leprosy look almost normal even though the bacilli are situated alongside the neuro-fibrillary ramifications. The present investigation further confirms that the sensory modalities are not much altered even though the nerve bundles are invaded by bacilli and cellular infiltration. In tuberculoid leprosy, the papillary ridges are practically non-existent and further the sub-epidermal nerve plexus is destroyed resulting in severely impaired sensory function.

Summary

1. Biopsies from distal pad of the fingers from 30 leprosy patients comprising 20 lepromatous and 10 tuberculoid were studied by cytological nerve staining methods.

2. It was found that the papillary ridges of the digital skin in lepromatous leprosy are very distinct. In early lepromatous leprosy, the intermediate ridges descend more in length into the corium

compared to advanced lepromatous leprosy where the ridges descend less in length. Extensive nerve fibres are seen embedded in these papillary ridges.

3. In tuberculoid leprosy, the intermediate papillary ridges do not descend into the corium and the ascending nerve fibres are mostly destroyed, practically resulting in severe sensory impairment.

4. The histological and functional considerations justify that the papillary ridges in lepromatous leprosy continue to act as an essential part of the tactile sense organ.

Acknowledgments

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REPORT OF CLINICAL TRIAL WITH ETISUL

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1 Name of Drug

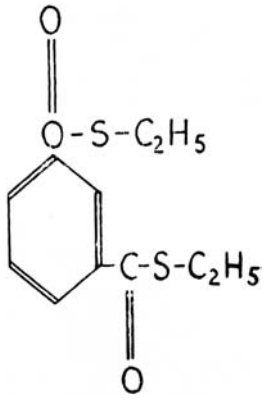
Etisul or Diethyl Dithiolisophthalate.

2 Chemistry and Composition

In 1950, DEL PIANTO claimed that a mixture of certain thiol compounds prevented the development of tuberculosis in infected guinea-pigs and in 1956 DAVIES *et al.* traced the active principle to ethyl mercaptan and compounds capable of forming it. This property was limited to the ethyl homologue and was evident almost solely *in vivo*. They concluded that a metabolite of ethyl mercaptan was the ultimate active agent and suggested thiol esters as the most useful group of compounds for the treatment of human disease.

DAVIES and DRIVER (1957) chose diethyl dithiolisophthalate (Etisul) as the most promising for therapeutic use. It has an anti-tuberculous effect in mice comparable to that of isonicotinic acid hydrazide and streptomycin and was most effective when injected subcutaneously or applied to the skin. It has since been added to the list of anti-leprotic drugs.

The chemical structure of Etisul is as follows:—



A product of Imperial Chemical Industries Ltd., Pharmaceuticals Division, England, Etisul is in the form of a soft cream, light yellow in colour with a garlic-like odour, containing diethyl dithiolisoph thalate (72 w/w), and perfumed with aromatic substances. It is packed in 5 g. tubes.

3. Efficacy and Versatility of Etisul

Specifically indicated for various types of leprosy, Etisul is of

particular value in the early stages. Its use hastens recovery and shortens the course of treatment. This is evidenced by the speedy decrease of the nodules and skin lesions, and the rapid marked reduction of a high bacterial index to negative.

Etisul can be applied safely by all persons irrespective of age and sex, and is free of contra-indications. When used together with other anti-leprotic drugs, such as DDS, Ciba 1906, Sulphetrone, etc., Etisul is not only very safe and free from any side effects, but also helps to attain a higher level of therapeutic efficacy.

In the case of lepra-reactive patients, Etisul either prevents same or reduces the severity. The onset of leprosy and its initial symptoms consist of the nodules, pigmentation or tubercles of the skin. By applying Etisul directly to the skin, its therapeutic efficacy is demonstrated by the speedy reduction of the external symptoms, which results in a favourable psychological effect on the patients.

4. Dosage and Mode of Application

Approximately 2.5 g. of Etisul was applied to the skin, 2 or 3 times per week. After application the ointment was massaged into the skin for duration of 20 minutes to hasten the dermal absorption. The massaged area was then exposed to the air for a period of 3 hours after which the area was washed with soap and water to remove the odour of the medicine.

5. Clinical Trials

(a) Eight cases were selected for clinical trial of Etisul in combination with sulphone drug or Ciba 1906 during the period of January to June 1960. These cases had previously received sulphones or Ciba 1906 for a period of at least 6 months and were selected because no improvement on these medications, their intolerance to optimal dosage of sulphones or due to lepra reactions.

(b) *Classification:* 4 lepromatous and 4 tuberculoid, one female tuberculoid patient and the remainder were males.

(c) *Results:* Lepromatous: Marked improvement, 3—marked improvement of skin lesions with a decrease in the bacterial index from severe to mild positive. One of these cases had far advanced lepromatous leprosy for more than 14 years and shown no improvement after receiving 2 years treatment according to the DDS regulation.

Moderate Improvement: 1—a young man with frequent lepra reaction who was intolerant to DDS and received Sulphetrone 3.0 gm. weekly. His bacterial index decreased from 4.5 to 3.8 and his lepra reaction subsided one month after the trial with Etisul.

Tuberculoid: Marked Improvement, 1—resolution of almost of his major tuberculoid macules.

Mild Improvement: 2 general improvement of skin lesions. One of these was a patient who had reactional tuberculoid leprosy. He was given Ciba 1906 because of severe toxicity to sulphone preparations. His improvement was mild with disappearance of the lepra reaction.

Periodical laboratory routine examinations including blood, urine and stool for the above 8 patient were performed during the past 6 months' trial of Etisul but none of them were found positive for toxic manifestation.

6. Conclusion

It has been noted that this drug has not produced a toxic reaction even in the two patients that had previous toxic reaction to the sulphones. It was also noted that there was change in the staining properties of the bacilli and rapid fall in the bacterial index with subsequent resolution of the lesions.

It can readily be used in conjunction with DDS, Sulphetrone and Ciba 1906. When combined in this way resolution was rapid and no drug resistance was noted. The most striking case was that of the man who was resistant to DDS treatment for a period of 2 years who revealed marked improvement and complete recovery from lepra reaction when his treatment was combined with Etisul.

7. Acknowledgements

We would like to thank the Imperial Chemical Industries Pharmaceutical Division, for their contribution of Etisul in this clinical trial.

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A PRELIMINARY REPORT ON THE TREATMENT OF LEPROSY WITH ETISUL IN A RURAL LEPROSY CENTRE

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Introduction

Sodium ethyl thiosulphate was first tried in leprosy by BERTACCINI in 1957 on 21 leprosy patients by the oral methods, and the results in the treatment of leprosy were encouraging. Also in 1957 T. F. DAVEY *et al.* of the Leprosy Research Unit, Uzuakoli, Eastern Nigeria tried Etisul first in one group of 18 patients and then in 22 patients, and reported a marked chemotherapeutic action and an apparent drug resistance after 3 months of the drug. There was no toxic action, but the odour of the drug was unpleasant (1959. Since then various workers have tried the drug, alone or combined with DDS, and reported favourably, such as C. M. ROSS *et al.* and M. F. LECHAT in 1960. The first report from India was that of N. MUKERJEE and S. GHOSH in October, 1960, who after a 6 months trial of the drug in 3 cases reported no appreciable improvement. DHARMENDRA—*et al.* also tried Etisul alone or combined with DDS and reported no accelerated bacteriological improvement except in 1 case, nor accelerated clinical improvement except in 2 nodular cases on Etisul combined with DDS. However we in this Centre, encouraged by the reports of DAVEY *et al.* began to try Etisul here at the end of 1959. The supply of the drug was small, so we began with only a few cases and were able to add a few more later.

The Aims of Etisul Therapy

Though the sulphones have become established as cheap, effective, and suitable for mass therapy, we have found a few disadvantages, viz. (1) The period of treatment needed to reach bacterial negativity is rather prolonged; (3 to 7 years); (2) the frequency of lepra reactions under sulphone therapy. Under Etisul we hoped to study and compare the pace of bacterial and clinical improvement in the lepromatous and intermediate kinds of leprosy and to find out if Etisul is better tolerated and less causative of reactions in lepromatous leprosy. We also hoped to find out if clinical improve-

ment of non-lepromatous cases is quicker with Etisul than with the sulphones.

Material for Study

We chose 17 patients of whom 9 were advanced lepromatous, 4 were lepromatous cases whose treatment had often been interrupted, 2 were non-lepromatous with marked lesions, and 2 were intermediate types (borderline or indeterminate). Most of all these patients had previous treatment for short or long periods. In 1959 we put 4 patients on Etisul treatment, 11 in 1960, and 2 in 1961. As regards drug combinations with Etisul, there was DDS in 7 cases, aqueous sulphetrone injections with INH in 4 cases and DPT in 2 cases. The *method* of Etisul therapy was by twice weekly inunction, first of half a tube twice a week, then a whole tube twice a week. In a very few cases, daily inunction of one tube was tried. A practical detail was that because of the unpleasant odour of the Etisul, the patients were found to be too eager to take a bath after inunction, hence a bath on the same day had to be forbidden for the bi-weekly inunctions and delayed to the evening in the case of daily inunctions.

Duration of Treatment

This was decided from observation of each individual case, and in effect the minimum period was 12 weeks and the maximum 65 weeks.

Results

The results were assessed clinically and bacteriologically. It was found that daily treatment with Etisul did not produce any better results than bi-weekly treatment. Combination with aqueous Sulphetrone did not seem to produce any difference in the pace of improvement. Etisul alone and Etisul combined with other drugs seemed about equal in this respect. The cessation of Etisul even for a short time seemed to worsen the condition. To use Etisul for a prolonged period does not seem to be beneficial, for after a rapid preliminary improvement, a stationary stage seems to develop. It was found that previous treatment with DDS seems to be better than starting with Etisul from the beginning. One fact which emerged clearly is that the clinical and bacterial improvement with Etisul is very rapid in comparison with sulphone therapy in lepromatous cases. In the 2 borderline cases there was very rapid clinical and bacterial improvement, which was more than could be expected from sulphones alone. Though this is only a preliminary report, we find that the results of treatment with Etisul are very encouraging.

Some Further Results, and Comparison with Sulphone Therapy

Of the 17 patients, there were 8 who had very little or practically no treatment prior to Etisul therapy, and of these 1 macular lepromatous patient had Etisul bi-weekly for 6 months. The clinical improvment in this patient was moderate and the bacterial index became reduced to one third of the original index by the 6 months of treatment. There was one lepromatous patient (L3) on bi-weekly Etisul, and DDS (irregularly), for 1 year, whose clinical improvement was slight but the bacterial index became reduced to one half of the original index. In a lepromatous case L2 on daily Etisul and DDS the clinical and bacterial improvement was slight. On the other hand, a borderline case in this group on bi-weekly Etisul plus DDS orally became free of signs and bacterially negative in 5 months. Similar remarkable bacteriological improvement in 5 months of Etisul (the index came from 2.2 to 1.6) was shown in a lepromatous case who had previously obtained a reduction from 3.75 to 2.2 in 18 months of treatment with DPT. There was another borderline case who became free of signs and negative bacterially after 5 months of bi-weekly Etisul in combination with daily injections of 0.5 ml. of 50% aqueous Sulphetrone, and INH orally in 150 mg. doses. In a lepromatous patient with repeated lepra reactions on previous sulphone therapy these were the same with Etisul therapy. One patient with tuberculoid leprosy showed remarkable improvement after 6 months of Etisul therapy, for seven eighths of the lesion area healed. On the whole, in these cases who had very little sulphone therapy prior to Etisul, only 2 out of the 5 lepromatous cases failed to respond satisfactorily these being cases of frequent lepra reactions. Thus 3 of the lepromatous cases showed good bacteriological improvement. The clinical and bacterial improvement in the 2 borderline cases was so good, as to attain negativity inside 6 months, and the tuberculoid case also attained very good clinical improvement in 6 months.

Of the 5 lepromatous cases who had Etisul bi-weekly or daily in combination with DDS, and in a few cases with aqueous Sulphetrone and INH, only 2 cases did not respond satisfactorily and these were lepra reaction cases of the frequent type.

Comparing the results of Etisul therapy with Sulphone therapy we studied the records of this Centre and found in 50 lepromatous cases on sulphones the average time to reduce the bacterial index to half the original was 22.3 months, and 44 months to reduce it to one quarter. Comparing this with our short series of cases on Etisul there has been a remarkably quick improvement in the bacterial condition of lepromatous cases, for the index reached one third of the original in 6 months and to half the original in 14 months time. For borderline cases in this Centre on sulphones it took an average of 29 months to reach bacterial negativity and 43 months for clinical

negativity, whereas, with Etisul, borderline cases became clinically and bacterially negative in a period of 5 months. The non-lepromatous cases have also responded with good clinical improvement in the short period of 6 months. However in reactive lepromatous cases of leprosy Etisul seems to have been no better than the sulphones. On the whole we conclude that Etisul therapy gives very quick and encouraging results in comparison with the sulphones. We bear in mind that a longer period of time is required for the full assessment of this drug, because there are the problems of drug resistance and relapses. The patients will be kept under observation, and further studies made and reported.

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[*Editor's Note:* The authors of this paper provided much other material in the shape of case notes, discussion of cases, illustrations etc. but under modern conditions of pressure on space it is regretted that much has had to be excluded. However it may be taken that their paper was presented well-documented in the original. *Editor*].

DITOPHAL* IN THE TREATMENT OF LEPROSY

By K. F. SCHALLER,
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and
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History

DAVIES and DRIVER (1956) investigated a claim that a mixture of certain thiol compounds prevented the development of tuberculosis in guinea-pigs (DEL PIANTO, 1950) and they discovered that the active principle involved was ethyl mercaptan. This property was possessed only by the ethyl homologue. They concluded that a derivative of ethyl mercaptan which was acceptable clinically and pharmaceutically and which liberated ethyl mercaptan in the body at the optimum rate should be effective against the mycobacterial diseases such as lupus, tuberculosis and leprosy. Ditophal was eventually chosen from about 400 ethyl mercaptan derivatives (DAVIES and DRIVER 1957).

The antituberculosis action of Ditophal is due to the release of ethyl mercaptan in the body, but neither compound shows any antituberculosis activity *in vitro*. Both are, however, very effective against intracellular bacteria, ethyl mercaptan inhibiting the growth of *M. tuberculosis* in an infected monocyte culture at 10γ/ml. The action of the ethyl mercaptan derivatives is antagonised by the methyl analogues and it is thought that ethyl mercaptan acts by interfering with a metabolic pathway which involves methyl or methylthio groups and which is present either in the monocyte or is part of the specific metabolism of the bacillus in the monocyte. The metabolism of Ditophal and of ethyl mercaptan has been studied in laboratory animals using C^{14} and S^{35}-labelled drug and almost all the administered drug has been accounted for without finding a metabolite with antituberculous activity (LOWE 1960, SNOW 1957).

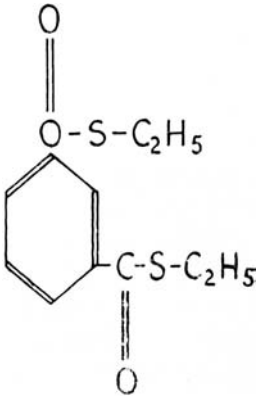
Ditophal is effective in laboratory animals when administered either parenterally or orally but it is more effective by the former route. Oral dosing gives rise to ethyl mercaptan in the gastrointestinal tract and some of this escapes giving an unpleasant smell. The drug has the unique property of being rapidly absorbed through the skin, thus offering a novel method of parenteral administration in leprosy while avoiding the difficulties associated with injection. This method of administration appeared to be peculiarly suited to the treatment of leprosy and lupus vulgaris and NAGUIB and ROBSON

* Ditophal ('Etisul' I.C.I.)

(1956) had already shown it to be outstandingly active against intracorneal infections of murine leprosy in the mouse and it was completely non-toxic.

Chemistry

Chemically Ditophal is diethyl-dithiolisophthalate. It is a bland oily liquid with a garlic-like odour and has the unique property of high systemic activity after percutaneous absorption (following inunction into the skin). For the purpose of inunction Ditophal is presented in either cream or liquid formulation based on an active-agent content of 5 g. per dose and suitably perfumed to mask the intrinsic odour.



Previous Clinical Work in Leprosy

Ditophal began to be clinically used in 1957. DAVEY (1958) first reported his early impressions from Nigeria to the VIIth International Congress of Leprology in Tokyo. Later (DAVEY and HOGERZEIL 1959, DAVEY 1959 & 1960) he published his experiences in greater detail and at a later stage of development. Ditophal was at first used alone, but later its greatest usefulness was found to lie in combined use with DDS or DPT (= SU 1906), where it materially reduced the period of time in which bacteriological and clinical improvement is obtained, compared with the length of time taken by these drugs, alone, to produce similar results. From experience, by trial and error, in a total of 133 patients DAVEY suggested that the best time to introduce Ditophal would be at a stage when full DDS maintenance dosage has been reached, and that the two drugs should then be given together for about 3 months.

LECHAT (1959) in the Belgian Congo obtained equally favourable results in 28 lepromatous cases and found the cream readily accepted by all his patients.

ROSS (1960) in Northern Nigeria found the bacterial index to

decline rapidly in 28 lepromatous and borderline cases, treated thrice weekly for 5 months.

GABRIEL (1959/60), in 8 patients in Queensland, obtained results which made him regard Ditophal as an extremely useful drug, since its use considerably reduces the time required for clinical improvement to become apparent and for a negative phase of the disease to be reached.

JAMISON and PALMER (1960) in 6 cases in Northern Nigeria, saw the bacilli disappear completely or almost completely, as well as finding marked histological improvement in leprous skin.

MCGREGOR (1961) used Ditophal alone for 12 weeks in 29 lepromatous cases in Sarawak (twice-weekly inunctions) and saw clinical and bacteriological improvement well beyond the level experienced with other drugs in that length of time. This rate of improvement persisted after change-over to basic treatment.

THANGARAJ and THANGARAJ (1961) obtained excellent results in 6 fresh lepromatous cases at Purulia, India, who received Ditophal together with parenteral sulphone.

All reports to date are unanimous in pointing to the lack of any side effects and signs of toxicity.

Personal Experiences

A trial of Ditophal in combination with DDS was begun at the Princess Zenebe Work Hospital, Addis Ababa in September 1959. 19 patients were treated, of whom 18 were of the lepromatous type and 1 was tuberculoid. There was only 1 female in the group, this being a case suffering from lepromatous leprosy, aged 40, with a history of one year's illness. The tuberculoid case was a man aged 26 with a history of two year's illness before admittance. The remainder of the patients were all lepromatous cases, age varying from 12–46 years and the duration of the disease from 1–7 years.

Diagnosis was made on clinical, bacteriological, immunological and histo-pathological grounds. None of the patients had received any previous treatment. Laboratory tests (bacteriological smears) and histo-pathology were also carried out in the Pasteur Institute, Addis Ababa. The treatment consisted of DDS which was gradually built up to a maintenance dose of 700 mg. per week (100 mg. daily), maintenance dosage being reached at the end of the third month. At this stage the patients started to receive Ditophal ointment by inunction, one tube (containing 5 grammes active agent) thrice weekly at equally spaced intervals. 15 cases were treated for the full period of one year (52 weeks), 3 cases were treated for 36 weeks and 1 case for 37 weeks only. The total dosage of DDS for those on one year's treatment amounted to 45 grammes and the total dosage of Ditophal to 156 tubes (780 g.).

Clinical details of cases

No. 20100—Male—30 years old.

Type of Disease: *Lepromatous leprosy*—4 years sick before admittance.
Lepromin: Negative. Tuberculin: Negative.
Weight: Slightly increased.

Hansen bacilli: On October, 1959 Nose: ++
Skin: ++++
On October, 1960 Nose: Negative
Skin: +

Sedimentation rate: January, 1960—70/115—October, 1960—30/60.

Decrease of bacilli after 6 months of treatment. Lesions less active
Patient feels better. *General conditions improved.*

TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 54.6 G.

No. 20284—Male—20 years old.

Type of Disease: *Lepromatous leprosy*—5 years sick before admittance.
Lepromin: Negative. Tuberculin: Negative
Weight: unchanged.

Hansen bacilli: On September, 1959 Nose: +++
Skin: ++++
On October, 1960 Nose: Negative
Skin: +

After 6 months considerable decrease of bacilli. Sedimentation rate improved.
Reaction after 3 months most probably due to D.D.S. Lepromatous lesions are flattened and less active. Patient feels better since 3 months trophic ulcer on left foot. *Clinically improved*

TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 54.5 G.

No. 18268—Male—20 years old

Type of Disease: *Lepromatous leprosy*—4 years sick before admittance.
Lepromin: Negative. Tuberculin: Negative.

Hansen bacilli: On September, 1959 Nose: +
Skin: +
On October, 1960 Nose: Negative
Skin: Negative

Weight increased by 5 kg.

Sedimentation rate: January, 1960—57/100 October, 1960—10/23

After 3 months of treatment patients suffer from *leprosy reaction.* Lepromatous lesions nearly disappeared. Patient feels better. *General conditions improved.*

TREATMENT: 51 weeks and 3 days. Total of Ditophal: 153 tubes (765 grammes)
Total of D.D.S.: 45.1 G.

No. 20148—Male—26 years old.

Type of Disease: *Tuberculoid leprosy*—2 years sick before admittance.
Weight: February, 6019, 63 kg. October, 1960, 65 kg.

Hansen bacilli: On October, 1959 Nose: Negative January, 1960:++
Skin: Negative
On October, 1960 Nose: Negative
Skin: Negative

Sedimentation rate: January, 1960—10/33

Loss of sensibility in the right hand of muscular strength. Rheumatic pains which occurred after 10th month of treatment. Now, conditions improved again. Superficial ulcers on both feet which are under treatment. After 3 months patient showed *reactionary phase* with bacilli ++, which was followed by a *general improvement.*

TREATMENT: 51 weeks Total of Ditophal: 153 tubes (765 grammes)
Total of D.D.S.: 45.4 G.

No. 20027—Male—23 years old.

Type of Disease: *Lepromatous leprosy*—5 years sick before admittance.
Lepromin: Negative. Tuberculin: Negative.

Hansen bacilli: On September, 1959 Nose: ++++
Skin: +++
On October, 1960 Nose: Negative
Skin: Negative

After 3 months treatment patient got reaction which is followed by decrease of bacilli. The sedimentation rate improved from 45/72 to 11/30. Patient feels much better but still complains of rheumatic pains on his legs and on his arms. Lepromatous lesions are flattened. *Clinically improved.*

TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.6 G.

No. 20258—Male—22 years old.

Type of Disease: *Lepromatous leprosy*—6 years sick before admittance.
Lepromin: Negative. Tuberculin: 13 mm.
Weight: unchanged.

Hansen bacilli: On October, 1959 Nose: ++
Skin: +++
On October, 1960 Nose: Negative
Skin: Negative

Sedimentation rate increased. Leprosy reaction occurred and was controlled by usual treatment. Lepromatous lesions are less active. Patient *clinically improved.*

TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.6 G.

No. 19835—Male—15 years old.

Type of Disease: *Lepromatous leprosy*—6 years sick before admittance.
Lepromin: Negative. Tuberculin: Negative.
Weight: 44 kg. now increased by 6 kg.

Hansen bacilli: On September, 1959 Nose: +
Skin: ++
On October, 1960 Nose: Negative
Skin: Negative

Lepromatous lesions do not show any more activity. Lepromatas are flattened. *Clinically* patient appears *improved* but complains still of burning sensations on both legs. Sedimentation rate: June 1960: 45/82 . October, 1960: 20/45.

TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.6 G.

No. 19973—Male—33 years old.

Type of Disease: *Lepromatous leprosy.*
Lepromin: Negative. Tuberculin: 5 mm.

Hansen bacilli: On September, 1959 Nose: +++
Skin: ++++
On October, 1960 Nose: Negative
Skin: Negative

Sedimentation rate: nor far from normal. Leprosy lesions on nose and skin disappeared; also the macular lesions on his back. Patient complains of disturbances in the sensibility on his left leg external surface. *Clinically improved.*

TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.8 G.

No. 20275—Male—27 years old.

Type of disease: *lepromatous leprosy*—2 years sick before admittance.
Tuberculine: Negative. Lepromin: Negative.

Hansen bacilli: On October, 1959 Skin: +++
Nose: ++
On May, 1960 Skin: ++
Nose: +++

Sedimentation rate: October, 1959 80/102. May, 1960 53/100

After 3 months *reaction* occurred followed by 2 *relapses.*
No marked *improvement.*

TREATMENT: 36 weeks Total of Ditophal 102 tubes (510 grammes)
Total of D.D.S. 32.4 G.

No. 20126—Male—28 years old.
Type of disease: *lepromatous leprosy*—5 years sick before admittance.
Lepromin: Negative. Tuberculin: 15 mm.
Hansen bacilli: On October, 1959 Skin: +++
Nose: ++++
On October, 1960 Skin: Negative
Nose: Negative
After 3*months reaction* most probably due to D.D.S. medication. Case is complicated by lymphogranuloma venereum like lesions. *Leprosy* clinically improved.
TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.6 G.

No. 20101—Male—28 years old.
Type of disease: *lepromatous leprosy*—7 years sick before admittance.
Tuberculin: Negative. Lepromin: Negative.
Sedimentation rate: October, 1959 30/55. July 1960 40/78.
Hansen bacilli: On October 1959 Nose: ++
Skin: +++
On July 1960 Nose: +
Skin: ++
After 3 months leprosy *reaction*, case did not show marked improvement.
TREATMENT: 36 weeks Total of Ditophal: 108 tubes (540 grammes)
Total of D.D.S.: 32.4 G.

No. 20247—Male—45 years of age.
Type of disease: *Lepromatous leprosy*—2 years sick before admittance.
Lepromin: Negative. Tuberculin: Negative.
Hansen bacilli: On October, 1960 Skin: +++
Nose: ++++
On July, 1960 Skin: ++
Nose: Negative
Sedimentation rate: October, 1959 80/120. July, 1960 40/68.
Reaction after 3 months treatment—*relapsed twice*, patient is moderately improved.
TREATMENT: 36 weeks Total of Ditophal: 120 tubes (600 grammes)
Total of D.D.S.: 32.4 G.

No. 19512—Male—54 years old.
Type of disease: *Lepromatous leprosy*—6 years sick before admittance.
Lepromin: Negative. Tuberculin: Negative.
Hansen bacilli: On August, 1959 Skin: ++++
Nose:
On November, 1960 Skin: Negative
Nose: Negative
Sedimentation rate: January, 1960 60/120. August, 1960 53/71
Lepra reaction after 3 months of treatment, patient increased weight, Ditophal was well tolerated, reaction most probably due to D.D.S. medication. *Clinically improved.*
TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.6 G.

No. 20110—Male—27 years of age.
Type of disease: *Lepromatous leprosy* 21/2 years sick before admittance.
Lepromin: Negative. Tuberculin: 10 mm.
Hansen bacilli: On October, 1959 Skin: +++
Nose: +++
On February, 1960 Skin: ++
Nose Negative
Patient tolerated well the treatment, but left the hospital after 5 months; therefore this case is not suitable for evaluation.
TREATMENT: 37 weeks Total of Ditophal: 111 tubes (555 grammes)
Total of D.D.S.: 33.3 G.

No. 20156—Female—40 years of age.
Type of disease: *Lepromatous leprosy*—1 year sick before admitted.
Lepromin: Negative. Tuberculin: 10 mm.
Hansen bacilli: On October, 1959 Skin: ++++
Nose: ++
On October, 1960 Skin: ++
Nose: +
Sedimentation rate October, 1959 40/75. October, 1960 15/37.
August 1960—*reaction* with two relapses. No considerable improvement.
TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.6 G.

No. 20186—Male—18 years of age.
Type of disease: *Lepromatous leprosy*—1½ years sick before admittance.
Tuberculin: Negative. Lepromin: Negative.
Hansen bacilli: On October, 1959 Skin: +++
Nose: +++
On October, 1960 Skin: Negative
Nose: Negative
Sedimentation rate: October, 1959 21/52. October 1960 20/47.
After 3 months of treatment patient developed *reaction*, most probably due to D.D.S. Patient feels better, *clinically improved.*
TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.6 G.

No. 20274—Male—46 years of gae.
Type of disease: *Lepromatous leprosy*—2 years sick before admittance.
Lepromin: Negative. Tuberculin: Netative.
Hansen bacilli: On October, 1959 Skin: ++++
Nose: ++++
On October, 1960 Skin: +
Nose: +
Sedimentation rate: October, 1959 95/120. October, 1906 130/135
After 3 months patient suffered from *reaction* which relapsed 6 times—case is *not improved.*
TREATMENT: 51 weeks Total of Ditophal: 153 tubes (765 grammes)
Total of D.D.S.: 45.5 G.

No. 20257—Male—12 years old.
Type of disease: *Lepromatous leprosy*—1 year sick before admittance.
Tuberculin: Negative. Lepromin: Negative.
Hansen bacilli: On October 1959 Skin. ++++
Nose: +++
On October, 1960 Skin: Negative
Nose: ++
Sedimentation rate: October, 1959 5/20. July, 1960 4/10.
October, 1960 *reaction* besides treatment was well tolerated. *Clinically improved.*
TREATMENT: 52 weeks Total of Ditophal: 156 tubes (780 grammes)
Total of D.D.S.: 45.6 G.

No. 20187—Male—15 years old.
Type of disease: *Lepromatous leprosy*—2 years sick before admittance.
Lepromin: Negative. Tuberculine: Negative.
Hansen bacilli: On October, 1959 Nose: ++
Skin: ++
On October, 1960, Nose: +
Skin: ++
Sedimentation rate: October, 1959 15/26. October, 1960. 25/45.
Clinically *no improvement.*
TREATMENT: 52 weeks Total of Ditophal: 152 tubes (760 grammes)
Total of D.D.S.: 45.6 G.

SYNOPSIS OF RESULTS WITH DITOPHAL IN LEPROMATOUS CASES

Case No.	*Total Dosage gms.*		*Period of Treatment*	*Results*		*No. of Reactions*	*Remarks*
	Ditophal	*DDS*	*weeks*	*Bacteriological*	*Clinical*		
20275	510	32.4	36	unchanged	unchanged	3	Reaction after 3 months, followed by 2 relapses
20101	540	32.4	36	decrease	unchanged	1	Reaction after 3 months
20247	600	32.4	36	decrease	slightly improved	3	Reaction after 3 months, followed by 2 relapses
20110	555	33.3	37	decrease	not evaluated	0	
20100	780	45.6	52	decrease	improved	0	
20284	780	45.5	52	decrease	improved	1	Reaction after 3 months
18268	765	45.1	51	negative	improved	1	Reaction after 3 months
20027	780	45.6	52	negative	improved	1	Reaction after 3 months, followed by disappearance of bacteria
20258	780	45.6	52	negative	improved	1	
19835	780	45.6	52	negative	improved	0	
19973	780	45.8	52	negative	improved	0	
20126	780	45.6	52	negative	improved	1	Reaction after 3 months. Case complicated by L.G.V.
19512	780	45.6	52	negative	improved	1	Reaction after 3 months
20156	780	45.6	52	decrease	unchanged	3	Reaction after 10 months' treatment, with 2 relapses
20186	780	45.6	52	negative	improved	1	Reaction after 3 months
20274	765	45.5	51	decrease	unchanged	7	Reaction after 3 months, with 6 relapses
20257	780	45.6	52	decrease	improved	1	Reaction after 12 months
20187	760	45.6	52	unchanged	unchanged	0	

Discussion of Results

Lepra Reactions Of the 18 lepromatous cases, details of which are consolidated in Table I, only 5 did not experience reactions. Nine cases had one reaction, 4 patients had 3 or more reactions. In most cases, the reaction occured at the end of three months' treatment with DDS just at the time they were starting Ditophal inunction. Their reactions, therefore, may have been provoked by the DDS medication, although the contributory effect of Ditophal cannot be excluded.

Bacterial Examination Routine examinations of smears were carried out every two weeks. Reduction in the number of bacilli was seen in 16 cases and of these 9 cases progressed to negativity. Two cases showed no change in bacterial density but 1 of these 2 cases was only treated for 35 weeks. Histopathological findings (biopsies were carried out at intervals of 3 months) were in general agreement with the bacterial smears.

Clinical Evaluation Of the 14 lepromatous cases treated for 52 weeks, 12 cases showed marked improvement, the remaining 2 cases were not improved at all. Of the 4 lepromatous patients treated for only 36–37 weeks, 2 cases were not improved at all, 1 was only slightly improved, and the 4th could not unfortunately be evaluated as he was a defaulter. The lack of improvement in this group may have been due to the fact that these cases were treated for a shorter period of time than the group treated for 52 weeks.

It is interesting to note that 1 case of tuberculoid leprosy, additional to the 18 cases already described treated for 52 weeks, suffered from a "reactionary phase" with bacillary index positive, followed by bacterial negativity and good clinical improvement when the reaction subsided.

Tolerance The inunction was well tolerated by all except 2 patients who showed skin reactions of papular type in the area inuncted. On withdrawal of Ditophal inunction for a few days, the reactions cleared up with no special treatment and they did not recur when inunctions were started again. No other side effects were seen with the drug.

Summary

1. The observation period in this investigation, being slightly more than one year, does not permit any final conclusion as to the lasting effect of the treatment.

2. The results so far indicate that the combined treatment, using DDS and Ditophal, yields more rapid results than in cases when standard treatment is given with DDS alone.

3. No evidence of drug resistance has been encountered in our cases.

4. Patients in our series will continue to receive DDS alone when they have completed the year's treatment of Ditophal and DDS, and these cases will continue to be kept under observation as out-patients.

5. We consider that further studies are desirable, in both in-patients and out-patients, with a view to finding which combination of standard drugs and Ditophal inunction and for how long, offers the best and most practicable way of treating the disease.

Acknowledgements

We are grateful to Health Officer Ato Zerihun Desta of Princess Zenebe Work Hospital, Addis Ababa, for assistance in following up our cases.

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LETTERS TO THE EDITOR

1. Dr. DE SOUZA-ARAUJO kindly sends the following Leprosy News from Brazil.

NEW CENTRE OF LEPROLOGY
MEDICAL SCHOOL, UNIVERSITY OF PARANÁ,
BRAZIL.

On 7th May, 1960 was inaugurated in Curitiba, capital of the State of Parana, Brazil, a new Centre of Leprology, under the Directorship of Dr. R. N. Miranda, Professor of Dermatology of the same University. The Centre has three sections: 1, Diagnosis and Therapy of Leprosy. 2. Teaching of Leprology and 3. Leprosy Investigation, with laboratories, museum and library. The Centre occupies the 1st floor of the Polyclinic Prof. Garcez do Nascimento. In 1960 the Centre gave his first Course on Leprology attended by 17 doctors to whom were given the Diploma of Leprologists. In the same year the Section of Investigation of the Centre co-operated with the XVII Annual Meeting of Brazilian Dermatologists. Address: Rua Ebano Pereira, No. 114 Curitiba, Parana, Brazil.

Teaching of Leprology

The Faculdade de Ciencias Medicas, University of Rio de Janeiro, is giving, since 1936, regular Courses of Leprology. This year 122 students of the 6th year of the medical curriculum are attending, divided into two groups, the advanced course in 40 lessons given by Professor Dr. H. C. de Souza-Araujo and his Assistants Dr. Avelino Miguez Alonso and Dr. João Baptista Risi. In connection with the chair of dermatology this year Dr. Avelino Miguez Alonso gave the programme of elementary leprology to 47 alumni of the 3rd year of the medical curriculum. In general the better classified students are employed in the Serviço Nacional de Lepra or in the Public Health Services of the States, where the control of Leprosy is enforced.

H. C. DE SOUZA-ARAUJO.

2. Dr. R. CHAUSSINAND writes these corrections.

"Je viens de recevoir le numéro d'octobre de la *Leprosy Review* et je constate que mon texte est pour-suivi par une malédiction, les arthropodes ne me portent pas bonheur. En effet, il y a deux fautes dont la dernière rend le texte incompréhensible:

p 274, 4e ligne il s'agit de 'lépromine' et non de 'léproline'.

p 274, 12e ligne, j'ai écrit 'eviction' et non 'evolution', C'est-à-dire exactement le contraire."

R. CHAUSSINAND

3. Dr. V. EKAMBARAM writes (sending corrections to his article).

"Sub: Article—Treatment of Reactions in Leprosy by Aq. Sulphetrone Injections and oral INH in a Rural Centre—Regarding.

Ref. *Leprosy Review* London—April 1961, Issue, p. 88.

V. Ekambaram, M.B.B.S.

State Leprosy Officer and Superintendent* of the Government Leprosy Treatment and Study Centre, Tirukoilur,

and

G. S. Gangadhar Sharma, M.B.B.S.

**Civil Assistant Surgeon, Government Leprosy Treatment and Study Centre, Tirukoilur.

* Not Director as mentioned

** Not a Civil Surgeon."

V. EKAMBARAM.

4. Dr. W. H. JOPLING states.

"Reference 'Vadrine Combined with Sulphone in the Treatment of Lepromatous Leprosy', *Leprosy Review*, July 1961, p. 189, figure 25 in the third column of the Table should read —25."

ABSTRACTS

A Proposito de um Caso de Manifestação Aguda da Lepra (a Case showing the Acute Leprosy). R. N. MIRANDA, *Revista Brazil de Leprologia*, **29**, 1, March 1961, pp. 3–12, 9 figs. in colour.

The author describes a case of lepromatous leprosy showing acute phenomena, namely fever, adenopathies, and leucocytosis, and erythematous and necrotic patterns of skin lesions The secretion of the skin lesions showed globi of *M. leprae* sited intracellularly in neutrophils. There was an acute episode lasting 30 days. Then the patient got well but entered a chronic diffuse lepromatous leprosy and new acute outbreaks. The author names this state "Acute Leprosy Manifestations," with 5 clinical varieties, nodular, polymorphous, suppurative, dimorphous, and necrotic. The present patient belongs to the necrotic class. He thinks these conditions result from a break in quiescent relations between *M. leprae* and the histiocytic cell, resulting in the liberation and dissemination of bacilli (either *in situ* or in the blood) or a new different reaction of the human body (shown by acute lesions, leucocytosis, and neutrophilia) which attempts to destroy the bacilli in the tissues and the disseminated bacilli. The author draws attention to the finding of the bacilli phagocytised by neutrophils, which he thinks to be the main event in acute leprosy manifestations. It points to a destruction of the disseminated bacilli, which is especially attained when there is pus in the lesions.

Viragem Lepromínica Após Retestagem em Crianças de 0 *a* 4 *Anos* (Lepromin Conversion after Retesting in Children 0–4 Years). L. M. BECHELLI and R. PAULA SOUZA. *Revista Brasil, de Leprologia*, **29**, 1, March 1961, pp. 13–18.

In 1953 and 1955 the authors studied with Ferraz and Quagliato the action of BCG in school children 5–9 and 10–14 years of age, who were free of leprosy and without known previous exposure. They found that retesting by lepromin converted from negative to positive in a proportion of cases practically similar to results obtained by oral BCG. In the present study, 46 children were retested for the Mitsuda reaction, of whom 12 were under 1 year old, 26 from 1–2 years of age, and 8 from 2–4 years. In the first test, of 46 children 0–4 years, 27 were negative, and 8 became positive 1+ and 11 positive 2 plus. The test was repeated after 40 days in the 46 children; in 41 children 14 were negative, 21 positive 1 plus, 5 positive 2 plus, and 1 positive 3 plus.

Lepromatosos em Tratamento Sulfonico (Lepromatous under Sulphone Treatment). R. QUAGLIATO, E. BERQUÓ, and W. LESER. *Revista Brasil de Leprologia*, **29**. 1, Mar. 1961, pp. 19–30.

The authors studied lepromatous patients discharged from sanatoria with the disease arrested, registered in the Campinas dispensary, negative on the occasion of their registry and up to 6 months afterwards kept under observation on a regime of sulphone treatment. It was found that the patient registered 1949–1952, expressed as cumulative coefficient of reactivation during $3\frac{1}{2}$ to $6\frac{1}{2}$ years of observation, were significantly more frequent than those registered from 1953–1959. In this latter period 1953–59 the cumulative coefficient of reactivation ran from 0.7% in the first half year to 26.4% at $6\frac{1}{2}$ years. It was noted that reactivated patients soon became negative again.

Alguns Aspectos da Nutricão em Face de Profilaxia e Tratamento da Lepra (Some Aspects of Nutrition Affecting Prophylaxis and Treatment of Leprosy). D. N. DA CUNHA, *Revista Brasil de Leprologia*, **29**, 1, Mar. 1961, pp. 31–33.

The author states that the leprosy bacillus is of limited pathogenicity but malnutrition of the body is a relevant factor in the beginning, clinical form, and later evolution of leprosy, whether human or experimental. Numerous papers show this, from the well-know studies of BADGER and SEBRELL with rats, wherein the incubation time for murine leprosy was shortened by Vitamin-B--deficient diets. Also, COLLIER inoculated leprotic material in monkeys on a diet containing sapotoxins and the disease rapidly appeared. Also AKROYD-KRISHNAN in Madras studied areas of high prevalence of leprosy, and found very varied nutritional deficiencies in families with a high incidence of leprosy among their members, these deficiencies being protein, mineral, vitamin, and even caloric in almost all cases investigated. On the other hand, simple improvement in the conditions of living had a decisive influence towards decrease of the leprosy infection, which attests the markedly social character of this disease, analogous to tuberculosis and chronic infections. It seems that the body resistance and the state of immunity of any infection are primarily and intimately bound up with the nutritional state of the individual, chiefly during childhood and in some cases even prenatal. Evidently other factors, such as heredity fatigue, intoxications, and nervous tension and anxiety, are responsible, but have less influence than the state of bodily nutrition. In the case of leprosy this method of approach is important in prophylaxis and treatment, and these factors can impede or retard the initial signs, can modify their evolution or accelerate their clinical cure. In leprosy the study of these influences on the peripheral nerves and skin has peculiar interest.

LUITHLEN supports this point of view. He says (1) nutrition can increase or diminish the reactivity of the skin against inflammation; (2) acid diets make the skin hypersensitive to external irritation and alkaline diets diminish the cutaneous reactivity; (3) skin reactivity is increased by an excess in the tissues of potassium and sodium, and is diminished by a greater concentration of magnesium and calcium. MAYER and SULZBERGER also confirm the influence of acid and alkaline diets, noting that guinea pigs can easily be sensitized to necarsphenamine in the summer, but not in the winter. When the guinea pigs had the winter diet during the summer, of dry forage, they attained a hyper-reactivity not only to necarsphenamine but also to other drugs.

In the prophylaxis of leprosy there should be given a balanced diet, normal in all respect for a higher protein value with the idea of favouring antibody development. In the ACKROYD-KRISHNAN investigation in Madras in 1937 there was a low protein level in the diets of the families studied, and the 42 g. per diem that each had was mostly vegetarian in origin. (It should be 1.5 g./kilo/day).

During the treatment of leprosy, diets poor in sodium and potassium and rich in calcium and magnesium, favour better internal conditions, diminish the incidence of reactional forms and the skin sensitivity, are more favourable to oedematous states. Acidity or alkalinity of the diets should be carefully studied. A slight disequilibrium in favour of alkalinity is beneficial. Because of numerous studies on the influence of certain vitamins on the skin and nerves, such as those of BADGER and SEBRELL, already cited, the diets prescribed in human leprosy, particularly in the predominantly neural forms, should possess a high level of vitamins B^1, A, and E. The evolution and duration of reactional phases in leprosy can be greatly influenced by a diet poor in salt, rich in glycines, proteins, and vitamins, with a light alkaline predominance, poor in fats and fried foods in general, a diet on the whole similar to that used in hepatic conditions. The proteins of milk and its derivatives are beneficial. RAMBO thinks that the diet in leprosy should be made up on the following basic principles:—(a) a variation in the dietary elements, to avoid monotony; (b) need for leaf vegatables; (c) raw foods, vegetables or citrus fruits, to maintain Vitamins A and C; (d) milk and its derivatives, as the chief source of protein and minerals; (e) a partial substitution of rice by oats, as a cereal rich in the B complex. Beer can also be used as a source of B complex.

Estudo Anãtomo-Clínico de 18 *Casos de Lepra Dimorfa* (*Study of* 18 *cases of Dimorphous Leprosy*). A. M. ALONSO and R. D. AZULAY, (paper delivered at the Symposium on Dimorphous Leprosy in Rio de Janeiro, Mar. 1960, under the auspices of the Brazilian Association of Leprology). *Arquivos Mineiros de*

Leprologia, **20,** 3, July 1960, pp. 303–313. Original in Portuguese. 5 photographs.

The authors conclude that the manner in which we combine the characteristic aspects of the 2 polar forms of leprosy in considering possible borderline leprosy varies greatly whether the point of view is clinical or histopathological. Both the typical cellular and tissue features of the polar types can co-exist entirely or partially in the same single lesion, and sometimes it is necessary to make several biopsies to confirm the case. Sometimes the clinical approach is without any evidence to cause one to suspect dimorphous cases, and the histopathological result from the laboratory is a complete surprise. At other times clinically it is possible to recognise a dimorphous case but this is not confirmed from the laboratory, with its limited microscopic field of examination. Though smears from the mucosa and lesions can be bacteriologically negative, the histology should always show the presence of acid-alcohol-fast germs in the lesions. The results of the lepromin test are variable, and can be positive, negative, or oscillating. From their experience the authors give in general a grave prognosis to such cases, but all their patients responded to modern therapy. A tuberculoid reactional eruption supervening in lepromatous cases under treatment must be related to this dimorphous kind of leprosy: the same applies to leprominic positivization which arises in patients considered lepromatous and negative bacteriologically after clinical improvement.

Consideracões Sõbre Casos Dimorfos (*Discussion of Dimorphous Cases*). A. C. PEREIRA (paper delivered at the Symposium on Dimorphous Leprosy in Rio de Janeiro, Mar. 1960, under the auspices of the Brazilian Association of Leprology). *Arquivos Mineiros de Leprologia*, **20,** 3, July 1960, 00. 231–331. Original in Portuguese. 12 photos.

The author concludes that the dimorphous group described by WADE and other authors is an intermediary clinical form of leprosy, and was studied in its transition from reactional tuberculoid towards lepromatous. Before the advent of the specific treatment the dimorphous form was also met with in the regression of lepromatous to tuberculoid. The dimorphous cases of greater diagnostic interest are those which show clinical symptoms of the lepromatous form with positive bacteriology and negative lepromin test, and these reveal a greater gravity. The leprologist working in the great centres in general has no other means but the clinical in order to classify his cases. Dimorphous cases need the help of histopathology in order to be diagnosed, and in fact do not give great anxiety when they are put under adequate treatment. The specific treatment of leprosy has modified our ideas as to what to do for the dimorphous case. The

author uses BCG to help to increase the resistance of the dimorphous case, chiefly in those who have weakly positive lepromin test, and thus obtains 33% of conversion or reinforcement of the reaction.

Considerõces Sôbre Casos Dimorphous (*Discussion of Dimorphous Cases*). I. R. VIEIRA (paper delivered at the Symphosium on Dimorphous Leprosy in Rio de Janeiro, Mar. 1960, under the Auspices of the Brazilian Association of Leprology). *Arquivos Mineiros de Leprologia*, **20,** 3: July 1960, pp. 342–353. Original in Portuguese.

The author thinks that lepromatous cases do not have the supervention of dimorphous aspects, nor do they have mutation phenomena. Central lepromatous cases decline in the direction of the indeterminate group passing through a stage which we can call pseudo-tuberculoid because of a transitory similarity with tuberculoid. In the reactional tuberculoid cases, chiefly those of an enduring permanent nature are those which we can define as borderline or dimorphouse and as part of a group of that nature.

Contribuicão a Estudo Clínico da Lepra Dimorfa (*Contribution to the Clinical Study of Dimorphous Leprosy*). NELSON SOUZA CAMPOS paper delivered at the Symposium on Dimorphous Leprosy in de Janeiro, Mar. 1960). *Arquivos Mineiros de Leprologia*, **20**, 3: July 1960, pp. 354–366. Original in Portuguese.

The author thinks from his study of the matter, with other colleagues, that the present group called dimorphous or borderline should be suppressed, re-establishing the true idea of the polar type. A new group should be created, joining the tuberculoid-in-reaction variety with the present dimorphous or borderline group. To denominate the new group to be created, author should remember the existing expressions (dimorphous, bipolar, interpolar, transitional, limitrophic, limitant). The expression "borderline" should be rejected, as being strange in our language. The expression "interpolar" which so far has had a less generalized use, should be favourably considered. He suggests that for greater precision the cases of the new group might be further designated as Xt (X being the general name of the new group) for cases belonging to present reactional tuberculoid leprosy, with positive Mitsuda reaction, and XI for cases of the present dimorphous group and the tuberculoid reactional variety with negative Mitsuda.

Contribuição ao Estudo Histopatológico da Lepra Dimorfa (*Contribution to the Histopathological Study of Dimorphous Leprosy*). P. RATH DE SOUZA. (paper delivered at the Symposium on Dimorphous Leprosy, Rio de Janeiro, Mar. 1960). *Arquivos Mineiros de* **20,** 3: July 1960; pp. 367–375. Original in Portuguese.

He has studied many cases and found a very mixed and variable cellular and tissue pathology. Along with NELSON SOUZA CAMPOS he makes the proposal of suppressing the present group of dimorphous or borderline and excluding the reactional tuberculoid variety, and creating a new group which fuses the tuberculoid reactional variety in the present dimorphous or borderline group, etc, (as in the paper by NELSON SOUZA CAMPOS.

Borderline Group under the Clinical Viewpoint. F. E. RABELLO, (paper delivered at the Symposium on Dimorphous Leprosy, Rio de Janeiro Mar. 1960). *Arquivos Mineiros de Leprologia*, **20**, 3, July 1960, pp.412–429. Original in English.

The author points out that the architecture of both polar forms may occur in the same patient, either both pictures standing together in the same skin area or in different places, or the lesions occur in different periods during the evolution of the disease. As to whether the tuberculoid and lepromatous granulomata keep their fundamental characteristics, the opinions of various authors are as follows: AZULAY does not report alterations in any structural aspect. So he found Virchow cells in 14 of 18 cases, well-defined tuberculoid granulomata in 11, and there were gigantocytes in 5 of these. The infiltrates were nodular, of focal or diffuse aspect, and the inflammatory reactions around the granulomata were scanty, of a few plasmocytes and lymphocytes. The tuberculoid part could be torpid or reactional. The diffusion of the cellular exudate varied, sometimes mainly lepromatous, sometimes mainly tuberculoid. Unna's band was present in 15 cases. The exudative process reached the epidermal limits in 6 cases. The mixed structure of T plus L in the same slide was noted in 11 cases. Diagnosis was made by examination of several slides of the same case. In all cases bacilli were positive, though in some cases only by histological examination. Y. R. VIERA thinks the existence of bipolar structure is doubtful. He never saw an undoubted lepromatous structure alongside the tuberculoid one. More often there is an encroachment or mild mixture of opposite structures. P. RATH DE SOUZA says that the bipolar granuloma are formed by cells of two types, epithelioid-like cells and histiocytes with vesicular nucleus and un-vacuolated cytoplasm, very similar to macrophages found in active lepromatous lesions. There is evident disagreement in these 3 reports, perhaps because of different conditions and circumstances. Interesting features also reported are (1) lipid researches by AZULAY, (2) the fibrous stroma granulomata reported by VIERA (3) the variations in length of bacilli noted by P. RATH DE SOUZA. Research on these lines should be developed, and agreement will finally be reached. The present disagreement on borderline leprosy may be only transient.

Lepra Borderline. J. GAY PRIETO, (paper delivered at the symposium on dimorphous leprosy held in Rio de Janeiro, Mar. 1960, under the auspices of the Brazilian Association of Leprology). *Arquivos Mineiros de Leprologia*, 20th year, No. 3, July 1960, pp.444–456. Original in Spanish.

This paper is a systematic study of all the opinions about Borderline leprosy. It concludes that borderline leprosy consists of a group of cases which are intermediary between the tuberculoid type and the lepromatous type, which exceptionally can evolve towards the lepromatous type. Borderline forms an unstable group, generally not malignant, which responds well to treatment, and its clinical manifestations are influenced well by the treatment made up of sulphone therapy, thiosemicarbazones, and corticosteroids. It contains 2 varieties, one nearer to the tuberculoid type, which is the reactional tuberculoid form or variety TR, the other nearer to the lepromatous type, with which some cases have a singular similarity, which is the genuine borderline variety or form.

Clinically it is characterized by elevated lesions of nodules, plaques, or bands or reddish or vinous colour, sometimes grayish, which sometimes resemble the tuberculoid reaction, and at other times especially in some regions like the lobules of the ears they resemble the lepromatous type. The general state can be affected. Almost always the bacilloscopy is positive, and is more intensely so as the case is nearer to the lepromatous type. The lepromin test is apt to be negative; in some cases it is positive although never intensely so. The so-called macular dimorphous form is neither a group nor a type. It is a habitual stage of evolution of indeterminate cases towards the lepromatous type, and exceptionally the designation has been given to cases of abrupt transformation of indeterminate into tuberculoid cases.

Simposio de Lepra Borderline (Symposium on Borderline Leprosy) O. SERRA: *Arquivos Mineiros de Leprologia* **20,** 3, July 1960 pp.456-460.

The author discusses several points raised by other authors, and gives his scheme of Borderline and its place in the classification of leprosy. For him the Tuberculoid polar form contains tuberculoid in reaction (Tr.), which is lepromin-positive. In between is the perilepromatous group (PL), including lepromin-negative pseudo-tuberculoids. On the right of that, verging towards the polar form L, is perilepromatous in reaction (pLr). The polar form L also contains leprotic reaction (Lr).

Lepra Borderline: Grupo Perilepromatouso, Satelite do Tipo L. (Borderline Leprosy: the Perilepromatous Group, Satellite of the

L Type). A. ROTBERG. *Arquivos Mineiros de Leprologia*, **20**, 3, July 1960 pp.463–469.

The author thinks that the lepromatous and tuberculoid types are very firm and stable and there has been no convincing evidence of transformation of one to the other, and there is no place for transitional, borderline, or dimorphous cases. These words only signify transition from L type to another usually anergic and often bacillary group called reactional tuberculoid. But only resistant lepromin-positive cases should be labelled "tuberculoid", The lepromin-negative or lepromin-doubtful often bacillary pseudo-tuberculoid cases (as well as their advanced stage, which is borderline) should be located within the L pole as a satellite group which may be called "perilepromatous".

Symposium on Leprosy 30 *Jan.* 1961 *at School of Tropical Medicine, Calcutta.* Bulletin of the Calcutta School of Tropical Medicine **9,** 2; April 1961, pp.69–79.

Dr. R. N. CHAUDURI gave the address of welcome at this symposium and said that leprosy research, control, and relief cannot be separated from each other, and that the introduction of the sulphone drugs has encouraged experiments with mass treatment and selective segregation. He recounted the origin and develpoment of the Calcutta School, and the work of MUIR and LOWE, and the great work of the School in training doctors. Lt. Gen. D. N. CHAKRAVARTI gave the inaugural address and mentioned that there are 300,000 leprosy patients in the State of West Bengal, and the rather poor response from the medical profession to come forward for antileprosy work. Dr. S. N. CHATTERJEE spoke on the Classification of Leprosy and gave a good historical review of its development and of the preferences of Indian leprologists on this subject. The Indian Classification divides leprosy into Non-lepromatous, Intermediate, and Lepromatous, and uses the terms maculo-anaesthetic, tuberculoid, polyneuritic, borderline, indeterminate, and of course lepromatous. Dr. S. GHOSH described clinical features and reaction in leprosy. Dr. S. KUNDU discussed helpfully the diagnosis and described the laboratory tests. Dr. S. P. BASU described radiological bone findings and angiography, and Dr. P. C. SEN GUPTA the pathological changes, including the histology, and the histology of reaction. Major E. J. SOMERSET described ocular lesions and their management, and Dr. P. N. KHOOSHOO the working of the national leprosy control scheme which runs on Five Year Plans and Control Centres and Subsidiary Centres and makes use of paramedical workers. Dr. N. MUKERJEE dealt with therapy and mentioned the standard drugs and many others under trial. Immunity in leprosy was dealt with by Dr. D. C. LAHIRI and experimental leprosy by Dr. N. C. DEY. The important

subject of surgery in leprosy was dealt with by Lt. Col. N. C. CHATTERJEE, and plastic surgery in leprosy by Dr. M. M. MUKHERJEE, and plastic surgery in leprosy by Dr. M. M. MUKHERJEE. Physiotherapy was discussed by Dr. S. K. SARKAR. The whole symposium report deserves to be studied carefully in the original, as it gives an encouraging impression of the high standard of present-day work by Indian leprologists and surgeons.

History of Antileprosy Legislation in South America in the Colonial Period. H. C. DE SOUZA-ARAUJO. Revista Brasileira de Medicina, **18,** 2; Feb. 1961.

For *Argentina* the author recounts that since 1596 there were imported African negroes who were subjects of leprosy, as well as white European immigrants. In 1778 the population of Buenos Aires was 37,130 of whom 30,196 were of Spanish and negro origin, mostly the latter, and there were 6,934 natives, Indians and mestizos and mulattoes. In 1778 control measures were established against endemic diseases, including leprosy, and leprosaria were set up in Santa Fe, Cordoba, Salta, and Tucuman. In Santa Fe in 1793 the total population of 2000 contained 14 leprosy patients who were begging from door to door, and 6 deaths from leprosy were registered. In *Brazil* leprosy was imported by European immigrants and especially by African slaves, about 50,000 of them from 1500 to 1591. In 1798 the total population was $3\frac{1}{4}$ million, of whom about 60% were Africans. Rio in 1741, Bahia in 1787, and Recife in 1789 had the first leprosaria, and most of the inmates were negroes or mulattoes. The first antileprosy law for Brazil was drawn up by a committee of 3 Lisbon doctors in 1741. The rules considered leprosy a contagious disease of greater or less degree according to its clinical type, and segregation of all confirmed cases was recommended without distinction. Leprosaria were established, with separation of sex and social classes. A health officer was given full authority to enforce the law. There was compulsory notification of cases, and special diagnostic examinations were given to distinguish leprosy from other diseases. In *Paraguay* leprosy was known from the beginning, and the natives were free of the disease. In *Peru* in 1563 there were a few cases in Lima, but the disease did not become prevalent. In *Venezuela* the first case of leprosy was reported in 1626, the patient being the Governor of the province, and other cases appeared between 1627 and 1640. Caracas leprosarium was founded in 1572. The author's *general conclusions* are (1) there was no pre-columbian leprosy; (2) the disease was introduced into South America by European colonists and African slaves; (3) the Colonial regulations considered leprosy contagious in varying degree; (4) there was compulsory notification and segregation of cases until cure; (5) cases of higher social class were allowed to be treated at home.

Statistical Records for the Medical Services of the Uganda Protectorate issued for 1959 give a *Summary of Leprosy Work*, pp.41–42 in 2 tables.

Details are given from the 4 provinces of Uganda, and for the 4 leprosaria (Buluba, Nyenga, Kumi-Ongino, and Kuluva). These are Mission leprosaria subsidised by Government and contain about 3000 patients. *The all-Uganda totals* given are: (1) The gross intake of patients for 1952–1959 was 71,147 patients; (2) Those diagnosed as leprosy patients were 57,424; (3) The total of cured 1952–1959 was 16,276; (4) Absentees over 1952–58 totalled 19,682, with about 8,000 in 1959; (5) In 1959 there were 31,444 patients attending; (6) There were 85 leprosy treatment villages and 126 other clinics, and the village accommodation for 4,069 patients had an average resident number of 3,320. There is no information given about the incidence of deformities.

(From the WHO Technical Report 16,221 Geneva, 1961 on Rehabilitation in Leprosy "those with physical disability represent one quarter of the total cases", EDITOR).

Incaparina (*low cost vegetable food with adequate protein developed against protein malnutrition.*) Report of the 12th Meeting of the Panamerican Health Organization, Washington, D.C. 1961. Document No. 36, pp. 286–291.

The Annex describes a vegetable food developed by the initiative and scientific work of INCAP for use in Central America in the prevention of protein malnutrition, which will be of great interest also to those in charge of leprosy institutions and leprosy control schemes. There are many parts of the world where protein malnutrition touches closely the therapeutic regimes used for leprosy, and the social background of the disease).

INCAP Vegetable Mixture 9 B contains 29% ground maize, 29% sorghum grain, 38% cottonseed flour, 3% Torula yeast, 1% calcium carbonate, and 4,500 I. U. of added Vitamin A per 100 g. It has a protein content of 27.5% and is similar to milk in protein quality. It can be produced at very low cost, (6.21 cents per pound at maximum production) and in the form of a thin gruel has proved to be highly acceptable in Central America. This formula and other similar ones will be known by the generic name of INCAPARINA. Under the Council of INCAP the public health authorities of any country in South America can be authorized to produce and distribute INCAPARINA, and it will be now feasible to produce for widespread use this low-cost, highly nutritive, and extremely acceptable vegetable mixture and use it in national efforts against protein malnutrition.