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CONTENTS

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EDITORIAL

1. Regeneration of Peripheral-Nerve Defects by Irradiated Homografts

There is a letter by LEONARD MARMOR on this subject in *The Lancet*, 1st June 1963, p. 1191, which seems of considerable importance to those engaged in rehabilitation of leprosy patients. Homografts have not previously been successful in man, because they provoke such a severe inflammatory response that the graft is reduced to a fibrous band.

Work at present in progress at the University of California at Los Angeles has resulted in the successful bridging of large gaps in peripheral nerves without the use of autografts. An inflammatory response can be prevented by the use of ionising radiations; and, in the preliminary experiments to be described here, high-energy electrons were used as the source of radiation.

MARMOR describes technique and two illustrative case reports in which encouraging results are given.

2. Therapy of Leprosy

In this issue there are several papers which add to and guide our knowledge of this field of leprosy. I draw attention to the paper by DR. M. F. R. WATERS on what might be described as a balanced trial of Macrocyclon in leprosy.

Also DR. TADASHI HIRAKO and HOSAKU SAKURAI pay attention chiefly to Sulfamethoxypyridazine.

DR. LOGINOV and his co-workers have been interested in a derivative of diphenylthiourea. This Russian work has been translated and reprinted in English so as to make available this interesting work in therapy.

CHEMOTHERAPEUTIC TRIALS IN LEPROSY

1. Comparative Trial of Macrocyclon plus Dapsone and Dapsone alone in the treatment of Lepromatous Leprosy

by M. F. R. WATERS, M.B., M.R.C.P.,
The Research Unit, Sungei Buloh Leprosarium, Malaya,
and
The National Institute for Medical Research, London, N.W.7.

Introduction

Active treatment has been available for leprosy since the introduction of sulphones in 1941 and many chemotherapeutic trials have been undertaken. However, with the exception of the series sponsored by the Leonard Wood Memorial (DOULL, 1954 and DOULL *et al.*, 1957, 1958, 1961) surprisingly few attempts have been made to apply the standard controlled methods evolved in other branches of medicine, in particular in tuberculosis by the British Medical Research Council (BRADFORD HILL, 1960). Therefore in the first drug trial undertaken by the Research Unit, Sungei Buloh Leprosarium, precise criteria for the selection, treatment and assessment of patients were written into the protocol. It was thereby hoped to elucidate which points were of greater and which were of minor importance in the design of leprosy drug trials. This object was likely to be assisted by choosing a drug which, for ethical reasons required to be tested for its additive effect in association with a known effective drug such as dapsone. Macrocyclon appeared a suitable compound for test.

Macrocyclon is one of the most active and least toxic members of a series of polyoxyethylene ethers developed by CORNFORTH and his colleagues (1951). It is a non-ionic compound of high molecular weight (about 4,000), with surface-acting properties. It has been shown to have considerable chemotherapeutic activity against experimental tuberculosis in the mouse (CORNFORTH *et al.*, 1955) and guinea-pig (REES, 1953) and there is evidence of a synergistic action with dihydrostreptomycin (SOLOTOROVSKY and GREGORY, 1952). It is concentrated in monocytes, and in cells of the reticulo-endothelial system (LOVELOCK and REES, 1955). When monocytes are taken from animals previously treated with macrocyclon, and infected with tubercle bacilli, no intracellular multiplication of bacilli takes place (MACKANESS, 1954). It has been suggested that the surface lipids of tubercle bacilli are modified by the drug, rendering the bacilli more sensitive to digestion within the phagocytic cells (LOVELOCK and REES).

Macrocyclon was used by BOYD *et al.* (1959) for treating 10 patients with far advanced pulmonary tuberculosis with resistant bacilli, for whom no other remedy was available. No serious toxic

or side effects were observed, although some rise in the plasma cholesterol was detected, and on very high dosage hypersensitivity rashes and pruritis occurred. No clinical improvement occurred. Perhaps the reason was that in human tuberculosis, unlike in experimental mouse tuberculosis, many bacilli are extracellular. However, both murine and human leprosy resemble murine tuberculosis in this respect, and since REES (1957) found that macrocyclon was therapeutically active in experimental murine leprosy, it was considered that a trial in human leprosy was indicated.

Organization and Conduct of the Trial

1. Observers

Responsibility for the day to day organization of the trial and for the clinical care of the patients was vested in the research leprologist. All leprosy clinical assessments were performed by an independent assessor, Dr. K. M. Reddy, who had no knowledge of the treatment received by any patient, and also practically no contact with any patient between assessments. Biopsies were sent, after fixation, by air mail to Dr. D.S. Ridley for histological assessment; no treatment details were given. All smears were taken and read by the research leprologist. This was because special studies were being made of the bacterial morphology, but in practice it was found impossible to remember details of any previous examination.

2. General Plan of the Trial

Lepromatous leprosy shows many diverse clinical appearances, and also little is known of the factors which affect prognosis and the rate of response to treatment. In an attempt to overcome these difficulties, and to learn more of the prognostic factors, first, a very careful classification of every patient was made using the method of RIDLEY and JOPLING (1962); and second, the system of 'like pairs', originally advocated by MUIR (1955) was introduced.

A total of fifty patients (twenty-five pairs) was included in the trial. All patients were treated in the research wards, and received a high protein diet. It was planned that the trial should last one year. Because of the slow rate of intake, however, the last three pairs were studied for six months only, whereas the first nine pairs were studied for a total of eighteen months.

3. Initial Selection of Patients

On admission, all new patients were examined by the research leprologist. Those satisfying the following criteria were provisionally selected:—

(*a*) Male Malays, Chinese and Indians (Dravidian), aged 15 years or more,

(*b*) having lepromatous leprosy, either pure or with only few atypical features,
(*c*) not having any other significant organic disease,
(*d*) having received no previous scientific treatment for leprosy,
(*e*) whose routine admission chest X-rays showed no evidence of active respiratory or cardiovascular disease.

The one exception to rule (*c*) was a patient with asymptomatic neurosyphilis who was treated with penicillin and bismuth. Stools from all patients were examined for worm infestation, which was treated whenever found.

In general, no patient who was thought to have received more than 10 injections of dapsone was admitted to the trial. Exceptions were two patients who had received 17 and 14 injections, respectively, who were paired together, a third, 16 injections, and a fourth who had received two courses of injections five and four years prior to admission. As far as could be ascertained, none of the remaining 46 patients had received more than 6 sulphone injections. Dapsone is routinely used in Government Clinics, but owing to local preference for injections, sulphone tablets are little used in Malaya, and it was considered unlikely that any patient had received them. Most patients had however taken traditional Malay, Chinese or Indian remedies.

4. Preliminary Investigations (of provisionally selected patients)

A. General

(i) Complete clinical and urine examinations.

(ii) Early morning and midday specimens of urine were examined for albumin daily for one week. Patients whose early morning specimens showed faint traces of albumin intermittently were included in the trial, those with midday albuminuria were excluded (McFADZEAN, 1962).

(iii) Weight.

(iv) Examination of sputum, if any.

(v) Haemoglobin; total and differential white blood count.

(vi) Serum protein, total and albumin/globulin ratio, and paper electrophoresis.

B. Leprosy

(i) Clinical examination of the leprosy condition.

(ii) Smears from both ear lobes, and from 4 to 6 selected skin sites from active lesions. These were examined for:

(*a*) the number of bacilli, the results being recorded using a logarithmic scale of 0 to 6+ (RIDLEY, 1958).

(*b*) morphology, recording the proportion of uniformly and of irregularly stained bacilli (WATERS and REES, 1962).

(iii) Two biopsies taken from typical active lesions (RIDLEY). Histopathologically all patients were 'pure lepromatous' (LL)

—40 patients—or 'near lepromatous' (BL) (RIDLEY and JOPLING). Histological diagnosis was determined before the allocation of treatment. The average pretreatment biopsy index for each patient always exceeded 0.5, save for both members of pair No. 9.

(iv) Colour photographs.

(v) Lepromin skin test, using 0.1 ml. Dharmendra type lepromin, the diameter of the area of induration being recorded in mm. at 48 and 72 hours, and at 1, 2, 3 and 4 weeks.

(vi) Intracutaneous tuberculin test, 1 tuberculin unit (TU) of RT 23, the diameter of the area of induration in mm. being read at 48 and 72 hours. Patients negative (0-4 mm.) to 1 TU were retested with 20 TU.

5. Initiation of the Trial

The preliminary investigations, save for the lepromin test, took 2-3 weeks to complete. Patients who failed in any requirement were discarded; moreover any patient, however otherwise suitable, who appeared likely to abscond, was also discarded.

Patients were collected together in pairs of the same race (save for pair No. 21, where a dark skinned Malay patient was paired with an Indian of very similar skin colour), having approximately the same intensity of leprosy infection. BL patients histopathologically, were paired with BL patients. In general any patient still unpaired two months from the day of admission was dropped as it was considered unethical to withhold treatment longer.

6. Initial Examination by the Independent Assessor

As suitable pairs were collected the patients were examined individually by the independent assessor who made detailed notes and charts of their lesions on the record sheets. Photographs and smear results, but not biopsy reports, were shown to the assessor.

Next the patients were submitted in their pairs and the assessor was required to reject any which he considered unsatisfactory. He then noted, and carefully recorded differences between the members of each pair, and the relative severity of their leprosy.

7. Allocation of Treatment

As each pair was accepted by the assessor the names of the two patients were placed in alphabetical order, the first being designated 'A', and the second 'B'. The letter ('A' or 'B') determining which patient was to receive the combined therapy (with dapsone plus macrocyclon) was contained in the next sealed envelope in a numbered series based on random sampling.

8. Chemotherapy

Twenty-five patients, one from each pair, received standard dapsone therapy (treatment group D); their partners were treated with dapsone plus macrocyclon (treatment group DM).

(i) *Dapsone (DDS).* All patients received intramuscular injections of dapsone in refined coconut oil twice weekly. The initial dose was 200 mg; after 6 weeks (12 injections) it was raised to 300 mg. twice weekly, for the remainder of the 12 months (93 injections).

(ii) *Macrocyclon.* Given by intravenous injection once a week as a 12.5% solution in saline, as follows:

1st week, 5 ml; 2nd week, 10 ml; 3rd week, 15 ml; 4th week and subsequently, 50 mg/Kg. body weight (range 14.9-29.4 ml.).

9. Observations throughout Treatment

A. General

(i) Haemoglobin and total white blood count—weekly.

(ii) Differential white blood count—monthly.

(iii) Urine—daily (early morning and midday specimens) for albumin.

(iv) Weight—weekly.

(v) Plasma cholesterol.

(vi) Serum proteins; total, A: G ratio and electrophoresis. (v) and (vi) were estimated monthly during the first 6 months, fortnightly during the second 6 months, and for pairs 1-16, a single final reading during the period 15-18 months.

B. Leprosy. Smears from 6-8 skin sites, including both ear lobes, every three months.

10. Assessment after Six Months' Treatment

A. General. Each patient had a complete clinical examination, chest X-ray, smears, lepromin and tuberculin tests, colour photographs comparable to the pretreatment photographs and two biopsies from sites adjoining the pretreatment biopsies.

B. Independent Assessor. Before examination of the patients, their antecubital fossae were covered by plaster so that the macrocyclon injection sites could not be recognized. The assessor first examined clinically each patient individually, making detailed notes and charts of lesions. All photographs and smear results were made available, but no biopsy reports.

After each examination, by reference to his pretreatment notes the assessor passed an opinion as to the change if any, in the patient's condition as follows:

No change.	Self explanatory.
Improvement.	1. Slight—some diminution in the size of lesions with or without some return to normal pigmentation.
	2. Moderate—between slight and marked.
	3. Marked—marked diminution in the size of lesions, and possible disappearance of some.

Deterioration. 1. Slight—some increase in the size of lesions.
2. Moderate—between slight and marked.
3. Marked—marked extension of lesions, with or without the appearance of new lesions.

Having completed the individual assessments of the 2 members of a pair, the assessor then examined both of them together. First he decided which patient was in the *better clinical condition*, stating whether the difference was slight, moderate or marked. Then using the detailed notes, charts and photographs, he decided which member of the pair had made the *greater progress since the start of treatment*, stating whether the difference in progress was slight, moderate or marked.

Finally, the assessor carefully recorded differences between the members of each pair, and in particular, the presence (including type and severity) or absence of any reaction. In all assessments care was taken to distinguish as far as possible between reactions and the underlying lepromatous state.

11. Assessment after Twelve Months' Treatment

At the completion of 12 months' treatment, pairs 1-22 were reassessed in the same way as at 6 months. In addition the assessor decided which member of each pair had made *the greater progress during the second 6 months* of treatment, and whether the difference in progress was slight, moderate or marked.

12. Assessment after Eighteen Months' Treatment

All patients remaining in pairs 1-9 were examined at 18 months in the same way as at 6 months. In addition, for the pairs remaining, the assessor decided which member of each pair had made *the greater progress during the third 6 months* of treatment, and whether the difference in progress was slight, moderate or marked.

13. Treatment of Reactions

Although it is generally agreed that 'lepra' reactions have become less severe and prolonged since the introduction of the sulphone drugs, erythema nodosum leprosum (ENL) has become more common and chemotherapy is frequently interrupted on the grounds that reduction or temporary cessation of treatment is beneficial (COCHRANE, 1959). As a result in past trials many patients received very different and smaller total dosages of sulphone from those prescribed in the relevant protocols. In this trial it was decided to treat patients in reaction with any or all of the standard drugs including corticosteroids as indicated, but not to alter the dose of the trial drugs (dapsone and macrocyclon) unless all attempts at controlling the reactions had otherwise failed. In fact, during the year of the trial, the dosage of dapsone and macrocyclon was never lowered;

one patient who was followed for 18 months received a reduced dose of dapsone, and two short rest periods during the third 6 months.

Drugs used in the treatment of reactions included stibophen, calcium laevulinate, chloroquine, antihistamines, teracycline, prednisolone, and corticotrophin.

14. Treatment received

The dosage prescribed was strictly adhered to. All patients received 52-53 injections of dapsone (14.4—14.7 g.) during the first 6 months, and those in group DM received 26 injections of macrocyclon. All patients studied in the second 6 months received a further 51-53 injections of dapsone (15.3-15.9 g). Those in group DM received a further 26 injections of macrocyclon. Total dapsone received over the 12 months was 29.7-30.3 g.

The thirteen patients who were followed for a further 6 months were whenever possible allowed to live in the settlement. The dosage of dapsone received during this third period was therefore more variable, totalling 10.0-17.5g. In addition, the patient who only received 10.0 g. of dapsone was also given 88.5 g. of thiambutosine (DPT, SU 1906).

Results

1. Scope of the Analysis

In the standard type of clinical trial, the results of the different assessments on individuals in one treatment group are compared with those obtained on patients in the other treatment group. By introducing the method of 'like pairs' it is also possible to analyse the differences in the results for the two members of each pair; in addition other results, e.g., relative clinical progress, which depend upon the direct comparison of the two members of each pair, may also be obtained.

Although twenty-five pairs were admitted, during the course of the trial a number of patients were dropped. Thus, not only were the total numbers of patients reduced in the two treatment groups, but also proportionately a greater number of pairs was lost. Because of this reduction in numbers the clinical, histological and bacteriological results are presented as comparisons of the individual assessments on the patients in the two treatment groups; and in addition as a comparison of the relative clinical progress of the members of each pair, which can only be studied on the pairs. Other possible advantages of pairing patients in leprosy drug trials will be the subject of a separate report.

2. Exclusions from the Analysis

A. Patients

Despite the careful selection process, 6 patients absconded for

longer or shorter periods, and were therefore excluded as follows:

(i) from all analyses: two D and one DM.

(ii) from the 12 months' analysis: one D.

(iii) from the 18 months' analysis: one D and one DM.

One D patient developed pulmonary tuberculosis after 3 months' treatment, and was discarded.

Both patients in pair 9 were excluded because they had very mild leprosy, and their pretreatment biopsy indices were less than 0.5.

The number of patients selected, and completing assessments, is shown in Table 1.

B. Pairs

Whenever a patient was lost from a pair, the remaining patient was kept in the trial for the subsequent group analysis. In addition at the end of the trial, but before analysis, the pairs were reconsidered especially with regard to their pretreatment clinical, bacteriological and histological characteristics. It was decided that the original LL and BL classification of 3 patients was incorrect, and that their pairing was unsatisfactory. Such retrospective reclassification is open to considerable criticism. However, this was the first time that the subdivision of lepromatous patients into LL and BL had been attempted in a trial using the method of 'like pairs'. While the ease and value of the subdivision has been proved in practice, it is not surprising that some uncertainty existed over a few patients until sufficient experience had been gained.

Table II shows the number of pairs used in the analysis at each assessment.

3. Clinical

The assessment of clinical progress in leprosy is notoriously subjective. Nevertheless, by analogy with the method of radiological assessment of progress used in the MEDICAL RESEARCH COUNCIL controlled clinical trials in pulmonary tuberculosis (1948 onwards) it was anticipated that the simple classification of progress made by the independent assessor would be sufficient to detect any significant differences in the two treatment groups.

For the statistical analysis, the progress recorded for each 6 months' period was scored as follows:

Improvement —	marked	3
	moderate	2
	slight	1
No change —		0
Deterioration —	slight	—1
	moderate	—2
	marked	—3

All patients showed clinical improvement of a lesser or greater degree. The results are given in Table III.

A. Analysis of Individuals

Even though there is some suggestion that group DM made rather better clinical progress over the period 0-12 months, none of the differences in the mean clinical progress between the two treatment series attains statistical significance at the 5% level.

B. Analysis of Pairs

Comparisons were made in the paired LL patients, both of their relative clinical condition at each successive examination and of their relative clinical progress over the various periods of the trial. (Table IV). No obvious differences were detected.

4. Histological

All patients showed histological improvement of a lesser or greater degree. The mean percentage decrease in the Biopsy Index was estimated for the period 0-6 months, 0-12 months, and 0-18 months, for the LL and BL patients. None of the mean differences between the two treatment groups attains statistical significance (Table V).

5. Bacteriological

(*a*) *Bacterial index*. The majority of pretreatment smears from all sites were 5+ (48%) and 4+ (42%). Only 2 patients had one pretreatment smear site negative (in both cases a compulsory ear site), one patient being BL (No. 21) and the other, although LL, having rapidly progressive disease which had probably recently changed from borderline to lepromatous leprosy, and whose subsequent smears were always positive.

All patients continued to have positive smears except for patient No. 21—both ears negative at 6 months—and another BL patient—one skin site at 18 months.

Every set of 6-8 smears from each patient was averaged. It was found that for 38 patients, 19 in both treatment groups including all BL patients, the end of treatment smears showed an improvement over the pretreatment results. In 3 patients (two DM, and one D) no change occurred in the smear results, and in 3 patients (one DM, and two D) the end of trial smears showed a slight deterioration.

The mean decrease in the average smear results, pretreatment compared with 3, 6, 9, 12 and 18 months is shown in Table VI. None of the mean differences between the two treatment groups attain statistical significance.

(*b*) *Bacterial morphology*. Considerable evidence has recently been produced that leprosy bacilli in biopsy homogenates or smears which stain irregularly by the Ziehl-Neelsen method are almost certainly dead. The evidence has been summaried by WATERS and REES who have shown that, under the conditions of this trial, a dramatic increase in the percentage of irregularly staining organisms

occurs in the smears of lepromatous patients following the commencement of chemotherapy. After only 6-9 months' treatment, on average 96% of bacilli showed irregular staining. Their report was based on the 39 patients in this trial who had had no, or virtually no treatment whatsoever for leprosy.

Table VII shows the mean decreases in percentage of uniformly stained bacilli for the 37 patients in whom the morphology was estimated throughout the trial. The decrease has been studied for the periods 0-3, 0-6, 0-9 and 0-12 months, to determine if combined therapy speeded the change in bacterial morphology, which the smears of all patients showed. None of the mean differences between the two treatment groups attains statistical significance. The periods 9-12, and 12-18 months have also been analysed to confirm that a constant minimum value of 3-4% had been reached, and to exclude the possibility of the emergence of drug resistance.

6. Reactions

(*a*) *Frequency and severity*. Reactions are now perhaps the major cause of disability to lepromatous patients on chemotherapy. The results have therefore been analysed to determine if treatment with macrocyclon affected their incidence and severity. Of the reactions experienced by the patients nearly all could be easily classified into the two groups suggested by JOPLING (1959) which we have termed 'Lepra Reaction' and ENL.

Lepra reactions. Occurred chiefly during the first 6 months of treatment and were graded as follows:

± doubtful reaction.

\+ definite mild reaction, usually responding to standard treatment.

\+\+ moderately severe reaction, usually responding poorly to standard therapy, and often requiring corticosteroids for a short period.

ENL. These reactions became more frequent as treatment progressed; 18 of 32 LL patients at 12 months, and 9 of 10 at 18 months had ENL. Of the four patients with ENL at entry to the trial, one had received 16 and another 6 injections of dapsone before admission. Thus only two patients developed ENL while yet untreated.

The severity of ENL has been graded as follows:

\+ mild, causing little discomfort, and responding to standard therapy.

\+\+ moderate, usually persistent, and not easily controlled by standard therapy. Where corticosteroids were given, the reaction was easily controlled by 5-15 mg. prednisolone daily.

+++ severe, persistent, causing very considerable discomfort, unaffected by standard therapy; requiring 20-35 mg. prednisolone daily for adequate control.

++++ very severe, usually of the necrotic type, difficult to control even with 35-45 mg. prednisolone daily.

The type and severity of reactions present at each assessment are shown in Table VIII. There is no significant difference between the DM and the D groups at the pretreatment, 6, and 18 months' assessments. At 12 months the greater number of D group LL patients in reaction (Lepra and ENL) compared with group DM is statistically significant at the 5% level. The corresponding difference for ENL reactions only is not significant, even when the intensity of these reactions is taken into account. It may therefore be that the addition of macrocyclon to standard sulphone therapy reduces slightly the incidence of reactions (Lepra and ENL), but this is uncertain.

(*b*) *Effect*

uncertainty whether reactions slow down the rate of improvement of patients on sulphone treatment. A further series of analyses have therefore been made to investigate if any of the assessments have been affected by the presence or absence of a reaction. Under the conditions of this trial there is no evidence of any association between the presence of a reaction and the decrease in the biopsy index, the decrease in the bacterial index, the decrease in the percentage of solid staining bacilli, and the assessment of clinical improvement over the periods 0-6 and 0-12 months. Thus the slight difference in clinical progress between the two treatment series over the period 0-12 months cannot be explained solely by the greater frequency of ENL at 12 months in the D group.

7. Comparison of LL and BL patients

The relative clinical progress of the 38 LL patients compared with the 6 BL patients is shown in Table IX. This shows that the BL patients made greater progress; the difference between the mean clinical progress of the patients with the two types of disease is significant at the 2% level at 0-6 months, and at the 1% level at 0-12 months. The differences in histological and bacteriological progress between the LL and BL patients has been shown in Tables IV and V, respectively. In addition, 19 of the 38 LL patients developed ENL but none of the 6 BL patients did.

8. Lepromin Tests

(*a*) *Pretreatment.* All early and late reactions were negative (less than 5 mm.) save for 2 LL and 2 BL patients who had 'doubtful' early readings of 5-6 mm.

(*b*) *Six months.* Five LL patients had early readings of 5-7 mm. One BL patient had an early reading of 8 mm. and another (No. 21) who was suffering from a lepra reaction had positive readings of 11 and 10 mm. at 48 and 72 hours, respectively. All other early readings and all late readings were negative.

(*c*) *Twelve months.* All early and late readings were negative save for early readings of 5-6 mm. in 6 LL patients, and 1 BL who alone had doubtful positive (5-8 mm.) readings at 0, 6 and 12 months.

9. Serum Proteins in relation to Therapy

The average serum protein figures, total, and percentage albumin and gamma globulin, have been estimated for the two treatment groups at 0, 6, 12 and 18 months. The decreases in the percentage of gamma globulin in the two treatment series has been analysed for the periods 0-6, 0-12, and 0-18 months, and none of the mean differences attains statistical significance.

10. Evidence of Drug Toxicity

(*a*) *Dapsone.* None of the patients showed any evidence of sensitivity.

(*b*) *Macrocyclon.*

(i) *Plasma cholesterol.* A significantly greater rise was detected in the plasma cholesterol of the DM patients than of the D patients. Within 3-6 months of completing the course of macrocyclon however, the level had returned to normal. The mean increases in plasma cholesterol are shown in Table X.

(ii) *Blood pressure.* No effect was detected.

(iii) *Haemoglobin.* The average pretreatment haemoglobin level for all patients was 14.1 g.% (range 17.3-10.9). A slight fall in average haemoglobin levels occurred in both treatment groups in LL patients (DM, 0.82 and D, 0.50 g.%) which was considered to be due partly to sulphone therapy and partly as a result of reactions. The lowest recorded figure in a patient with ENL was 9.1 g.%.

(iv) *White blood count.* No leucopenia was detected. Leucocytosis often occurred in ENL, and also occasionally in response to intercurrent infections.

(*v*) *Albuminuria.* A faint trace of albumin was detected at times in early morning specimens of urine from all patients. There was no evidence to connect it with therapy.

(vi) *Weight.* Nearly all patients were in a satisfactory state of nutrition on admission. The average weight gained in one year was $4\frac{1}{4}$ lb. for the DM group, and $2\frac{1}{4}$ lb. for D group.

(vii) *Skin rashes.* Three patients in the DM group had brief episodes of irritant skin rashes which cleared without interruption of macrocyclon treatment.

Discussion

Under the conditions of the trial here reported there is no evidence that the addition of macrocyclon to parenteral dapsone therapy significantly alters the clinical, histological or bacteriological rates of response to treatment. Even the finding that the overall incidence of 'lepra' and erythema nodosum leprosum (ENL) reactions was significantly lower in the combined therapy (DM) group must be treated with some reserve. For the mechanisms of the two types of reaction are almost certainly very different in nature, and the analyses of their incidence separately (as opposed to the combined incidence) did not yield statistically significant results. It is proposed to discuss in a further report the value of testing new anti-leprosy drugs in combination with dapsone, together with possible refinements of the methods used in this trial.

Leprosy in Malaya, especially in the Chinese and Malay races is very unstable. There is a marked tendency, in the absence of chemotherapy, for patients to deteriorate towards the lepromatous end of the spectrum or 'continuum' of WADE (1961). The majority of undoubted lepromatous patients at Sungei Buloh Leprosarium are found on careful clinical examination to have one or more plaques or annular lesions possessing the characteristics of borderline leprosy, and nerve enlargement is often not completely bilaterally symmetrical. Yet in their rate of progress and ultimate prognosis, and also in their liability to develop ENL they resemble patients with clinically 'pure' lepromatous leprosy. It was therefore essential in this trial to make a careful classification of the patients studied, by using all available prognostic factors, clinical, histological, bacteriological and immunological. The system of classification for research purposes suggested by RIDLEY and JOPLING has been adopted, and has worked well in practice. It was decided to admit near-lepromatous (BL) as well as pure lepromatous (LL) patients to the trial, and once experience had been gained, there was remarkably little disagreement over the correct classification of individuals.

The relative severity of the disease in untreated patients admitted to Sungei Buloh is probably related to the frequency with which lepromatous leprosy evolves from borderline leprosy in Malaya. The majority of lepromatous patients are already at the moderately severe (L_2) stage, even when the history of symmetrical spread is of only a few months duration. Early pure lepromatous patients (L_1) are relatively uncommon, and were in effect excluded from this trial as their biopsy indices are usually less than 0.5. Thus all LL patients studied were at the L_2 or L_3 stages of the disease.

With the facilities available at Sungei Buloh leprosarium it was considered safe to give a high initial dose of dapsone (200 mg. twice weekly), and to increase to full dosage after only six weeks. This high

initial dose schedule probably accelerated and made more obvious the degenerative changes in the morphology of *Mycobacterium leprae* in our patients, in this way aiding the quantitative morphological assessments. No patient appears to have suffered any ill effects from the prescribed dose schedule. No case of sulphone sensitivity occurred, and the overall incidence of ENL (50% of LL patients) is similar to other treatment series (DOULL *et al.*, 1957, 1958, 1961).

Similarly, the decision to keep patients with ENL on full anti-leprosy treatment (giving corticosteroids as and when required), while not generally advocated, has enabled the relationship between reactions and the response to treatment to be specially studied. As a result it would appear that the poorer response of ENL patients to chemotherapy which has been widely reported (DOULL *et al.*, 1957, DAVISON and KOOIJ, 1957) is not due to a direct action of the ENL but to the reduction or cessation of active treatment compelled by the reaction.

Because of the finding in this trial that after 9 months' treatment 96% of bacilli in skin smears are almost certainly dead, it has been suggested that drugs which assist in the breakdown of effete mycobacteria might be of special value in lepromatous leprosy. Because macrocyclon has surface-acting properties, alters the sensitivity of red blood corpuscles to thermal shock, is thought on theoretical grounds to act on the mycobacterial cell wall (LOVELOCK and REES), and is retained in monocytes for several weeks, it was decided relatively late in the trial to study a number of patients for a third 6 months' period. This was written into the protocol, and pairs 1-9 were assessed at 18 months after commencing treatment. There was, however, no evidence either of a late effect of macrocyclon, or that macrocyclon speeded the destruction and removal by the body of fragmented and granular bacilli.

Summary

1. A controlled clinical trial is reported of combined dapsone and macrocyclon therapy compared with dapsone alone in the treatment of pure lepromatous and near lepromatous leprosy.

2. Twenty-five untreated, matched pairs were admitted to the trial, and the final analysis was made on 16 pairs and 44 patients, 21 of whom received dapsone, and 23 combined therapy.

3. The treatment regime was unusual in that, (*a*) a high initial dose of dapsone (200 mg. twice weekly by injection) was used; (*b*) the full dose schedule was maintained despite the occurrence of erythema nodosum leprosum.

4. Under the carefully controlled conditions of the trial it was concluded that

(*a*) All 44 patients showed improvement,

(*b*) the addition of macrocyclon to dapsone treatment failed to increase the rate of clinical, histological or bacteriological movement,

(*c*) the addition of macrocyclon may have reduced the incidence of reactions,

(*d*) all patients showed a dramatic fall in the percentage of solid staining organisms in skin smears, and after 9 months on average 96% of leprosy bacilli examined were irregularly stained.

Acknowledgements

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TABLE I

Number of patients selected and completing assessments

Assessment / *Type of Leprosy*	*Pretreatment*			*6 months*			*12 months*			*18 months*		
	LL	*BL*	*Total*	*LL*	*BL*	*Total*	*LL*	*BL*	*Total*	*LL*	*BL*	*Total*
Treatment Group												
DM	21	4	25	20	3	23	17	3	20	5	2	7
D	19	6	25	18	3	21	15	2	17	5	1	6

TABLE II

Number of pairs at each assessment

Assessment	*6 months*			*12 months*			*18 months*		
Type of Leprosy	*LL*	*BL*	*Total*	*LL*	*BL*	*Total*	*LL*	*BL*	*Total*
No. of pairs	16	1	17	13	1	14	4	—	4

TABLE III

Scores of Clinical Progress

Type of disease	*Period (months)*	*Treatment series*	*No. of Patients*	*Mean Score*	*SD*	*SEm*
LL	0—6	DM	20	1.30	0.47	0.11
		D	18	1.22	0.55	0.13
	6—12	DM	17	1.24	0.44	0.11
		D	15	0.93	0.26	0.07
	0—12*	DM	17	2.59	0.71	0.17
		D	15	2.20	0.68	0.17
	12—18	DM	5	1.00	0.00	0.00
		D	5	0.80	0.45	0.20
BL	0—6	DM	3	1.67	0.58	0.33
		D	3	2.00	0.00	0.00
	6—12	DM	3	1.67	0.58	0.33
		D	2	1.50	0.71	0.50
	0—12*	DM	3	3.33	1.15	0.67
		D	2	3.50	0.71	0.50
	12—18	DM	2	1.50	0.71	0.50
		D	1	1.00	0.00	0.00

* *sum* of readings for 0—6 and 6—12 months

TABLE IV

Comparison in paired LL patients of clinical progress in various periods

Period (months)	*No. of pairs*	*Patient on DM better than patient on D*			*No Difference*	*Patient on D better than Patient on DM*		
		marked 3	*moderate 2*	*slight 1*	*0*	*slight 1*	*moderate 2*	*marked 3*
0—6	16	0	1	1	8	6	0	0
6—12	13	0	2	5	2	2	2	0
0—12	13	0	1	7	3	2	0	0
12—18	4	0	1	1	2	0	0	0
0—18	4	0	0	1	3	0	0	0

There is no obvious difference between the clinical effects of the two treatments in paired patients

TABLE V

Percentage decrease in Biopsy Index

Type of disease	*Period (months)*	*Treatment series*	*No. of Patients*	*Mean Decrease*	*SD*	*SEm*
LL	0—6	DM	20	30.0	30.23	6.76
		D	18	23.4	56.06	13.21
	0—12	DM	17	51.3	21.06	5.11
		D	14	51.2	27.20	7.27
	0—18	DM	5	55.6	37.70	16.86
		D	4	75.6	18.52	9.26
BL	0—6	DM	3	6.3	21.96	12.68
		D	3	47.6	38.52	22.24
	0—12	DM	3	82.2	18.15	10.48
		D	2	73.8	22.98	16.25
	0—18	DM	2	87.8	10.96	7.75
		D	0	—	—	—

None of the above mean differences between the two treatment series attains statistical significance

TABLE VI

Decreases in Bacterial Index

Type of disease	*Period (months)*	*Treatment series*	*No. of Patients*	*Mean Decrease*	*SD*	*SEm*
LL	0—3	DM	20	0.04	0.28	0.06
		D	18	−0.01	0.40	0.09
	0—6	DM	20	0.24	0.32	0.07
		D	18	0.08	0.34	0.08
	0—9	DM	17	0.44	0.46	0.11
		D	15	0.22	0.50	0.13
	0—12	DM	17	0.56	0.48	0.12
		D	15	0.25	0.46	0.12
	0—18	DM	5	0.48	0.41	0.18
		D	5	0.50	0.34	0.15
BL	0—3	DM	3	0.53	0.47	0.27
		D	3	0.07	0.59	0.34
	0—6	DM	3	0.53	0.40	0.23
		D	3	0.43	0.75	0.43
	0—9	DM	3	1.07	0.60	0.35
		D	2	0.50	0.57	0.40
	0—12	DM	3	1.20	0.72	0.42
		D	2	0.30	0.14	0.10
	0—18	DM	2	1.75	1.06	0.75
		D	1	1.00	0.00	0.00

None of the above mean differences between the two treatment series attains statistical significance

TABLE VII

Decreases in Percentage of Uniformly Stained Bacilli

Type of disease	*Period (months)*	*Treatment series*	*No. of Patients*	*Mean Decrease*	*SD*	*SEm*
LL	0—3	DM	18	34.2	19.5	4.6
		D	16	37.3	23.0	5.7
	0—6	DM	18	42.1	23.8	5.6
		D	16	45.2	25.5	6.4
	0—9	DM	15	44.9	24.4	6.3
		D	13	48.4	25.9	7.2
	0—12	DM	15	44.0	24.0	6.2
		D	13	48.3	25.1	6.9
BL	0—3	DM	1	42.0	—	—
		D	2	30.5	34.6	24.5
	0—6	DM	1	55.0	—	—
		D	2	33.5	37.5	26.5
	0—9	DM	1	56.0	—	—
		D	1	7.0	—	—
	0—12	DM	1	53.0	—	—
		D	1	6.0	—	—

None of the above mean differences between the two treatment series attains statistical significance

TABLE VIII

Frequency and intensity of Reactions of the two types

Type of disease	*Examination*	*Treatment series*	*No. of patients*	*Type and intensity of Reaction*							
				ENL				*LEPRA*			
				+	++	+++	++++	±	+	++	*None*
LL	Pretreatment	DM	20	1	2	0	0	5	3	0	9
		D	18	1	0	0	0	7	4	0	6
	6 months	DM	20	3	1	2	0	3	1	0	10
		D	18	0	3	0	1	2	1	1	10
	12 months	DM	17	2	4	1	0	1	0	0	9
		D	15	4	3	1	3	1	1	0	2
	18 months	DM	5	3	1	0	0	0	0	0	1
		D	5	1	3	0	1	0	0	0	0
BL	Pretreatment	DM	3	0	0	0	0	2	0	0	1
		D	3	0	0	0	0	0	2	0	1
	6 months	DM	3	0	0	0	0	0	0	0	3
		D	3	0	0	0	0	1	0	0	2
	12 months	DM	3	0	0	0	0	1	0	0	2
		D	2	0	0	0	0	0	0	1	1
	18 months	DM	2	0	0	0	0	0	0	0	2
		D	1	0	0	0	0	0	0	0	1

The difference between the two treatment series in the proportion of LL patients in reaction (ENL or Lepra) at 12 months is statically significant at the 5% level. The corresponding difference for ENL reactions only is not significant, even when the intensity of these reactions is taken into account

TABLE IX

Relative clinical progress of LL and BL patients

Period (months)	*Mean score for clinical progress*	
	LL	*BL*
0—6	1.26	1.83
0—12*	2.41	3.40

*Based on sum of readings for 0—6 and 6—12 months

The difference between the mean clinical progress of patients with the two types of disease is significant at the 2% level at 0—6 months and at the 1% level at 0—12 months

TABLE X

Increases in plasma cholesterol
(both types of disease combined)

Period (months)	*Treatment series*	*Number of patients*	*Mean Increase†*	*SD*	*SEm*
0—6	DM	23	58.4	53.8	11.2
	D	21	25.8	51.7	11.3
0—12	DM	20	69.0	58.0	13.0
	D	17	13.1	65.0	15.8
0—18*	DM	15	12.3	32.8	8.5
	D	12	26.0	59.3	17.1

† mg. per cent

* The '18-month' readings were made between 15 and 18 months

The mean increase in the DM series was significantly greater than that in the D series at 0—6 months (at the 5% level) and at 0—12 months (at the 1% level)

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CHEMOTHERAPY OF LEPROSY CHIEFLY WITH SULFAMETHOXYPYRIDAZINE

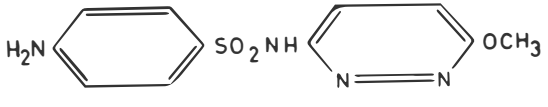
by TADASHI HIRAKO, M.D.* and HOSAKU SAKURAI, M.D.†

In Japan, the use of chemotherapy with sulphonamide such as Promine DDS, etc., for leprosy has been widely practised since about 1950. This type of treatment has been so successful, that along with the merit of early-diagnosis and treatment, there is a good possibility of the leprosy patients being allowed to return to their communities after treatment. However in 1955, we found some relapsing cases, and the majority of them were resistant to Promine. In our leprosarium (Tama Zenshoen), about 1200 patients were admitted and there were approximately 30 relapsing cases each year (Table 1). Because of this we changed to use of DDS for these Promine-resistant cases. These cases improved temporarily, but soon became resistant to DDS. Next, we treated them by thiourea derivatives, but they became non-effective after two years treatment, and drug resistance once again appeared. One of the interesting things noted on the chemotherapy of leprosy is the following: Promine as you know, is one of the DDS derivatives, nevertheless, DDS is effective in Promine-resistant relapsing cases. This has been observed not only in sulphonamides but also in thiourea derivatives. Similarly, cases which are resistant to Dimethylamino T.C. (TAMEMASA) were susceptible to Butoxy T.C. (BUU HOI). These features of lepra bacilli are not seen in other bacteria. This situation encourages the trial of Sulfamethoxypyridazine for relapsing cases as well as new cases of leprosy.

TABLE 1. RELAPSING CASES BY YEARS.

Type	*Year* '54	'55	'56	'57	'58	'59	'60	'61
Lepromatous	13	63	26	21	39	41	48	40
Non-Lepromatous	2	3	2	2	3	0	3	1

Sulfamethoxypyridazine also has been useful for tuberculosis, so we felt that it will be beneficial for leprosy. This is another reason for using Sulfamethoxypyridazine as a treatment for leprosy.



Sulfamethoxypyridazine "Lederkyn"

* National Leprosarium Tamazenshoen.

† National Leprosarium Nagashima aiseien.

Materials and methods

(1) 0.75 gm every other day, given orally to 55 cases.

(2) 0.5 gm daily, given orally to 45 cases.

The number of treated cases with Sulfamethoxypyridazine was 100, and all were lepromatous leprosy. (Table 2).

TABLE 2. NUMBER OF CASES

	Method I	*II*	*Total*
1. New case	13	2	15
2. Relapsing case			
(i) simple relapsing case	0	3	3
(ii) drug-resistant relapsing case	24	49	73
3. Cases that had failed to become bacteriologically negative by other drugs and changed over to 'Lederkin'	4	0	4
4. Others	4	1	5
	45	55	100

Periods of medications

	Method I	*II*	*Total*
24 Months	0	9	9
18 „	3	7	10
12 „	10	8	18
6 „	21	8	29
3 „	5	15	20
less than 3 Months	6	8	14
	45	55	100

Evaluation of treatment results

	Method I	*II*	*Total*
Effective	42	54	96
Ineffective	3	1	4
(Epithelioid cell react.)	(4)	(5)	(9)
	45	55	100

Discussion

This drug was effective to both new and old cases. Erythema nodosum leprosum has been observed in several cases.

For the past two years or so, on patients in which Sulfamethoxypyridazine has been used for antileprotic purpose, no particular side effects including deleterious actions on the liver, kidney, or hematopoietic system have been observed. Some of the patients have complained of gastric disturbance due to the oral administrations, but this complaint has not been such as would call for discontinuation of treatment.

Drug resistance appeared from about one and a half year to two years and only a small number of cases have shown relapsing (Fig. 1).

During the treatment with Sulfamethoxypyridazine, Epithelioid cell reaction or so called Pseudoexacerbation de Souza Lima was observed sometimes. When this reaction occurred in lepromatous

cases, all clinical findings became similar with those of tuberculoid cases. Lepromin reaction became positive, serologic lepra reaction became positive to negative and also, bacilli soon became negative.

After close examination of the early discharged lepromatous cases, it was found that almost all these patients revealed that Epithelioid cell reaction was regarded to be Pseudoexacerbation.

Therefore, we think that it is necessary for the treatment of chronic inflammatory diseases such as tuberculosis, leprosy, etc., to use not only drugs, but also to use this biological action. Utilization of biological action as a means of cure, helps speed up the course of treatment of such chronic inflammatory diseases.

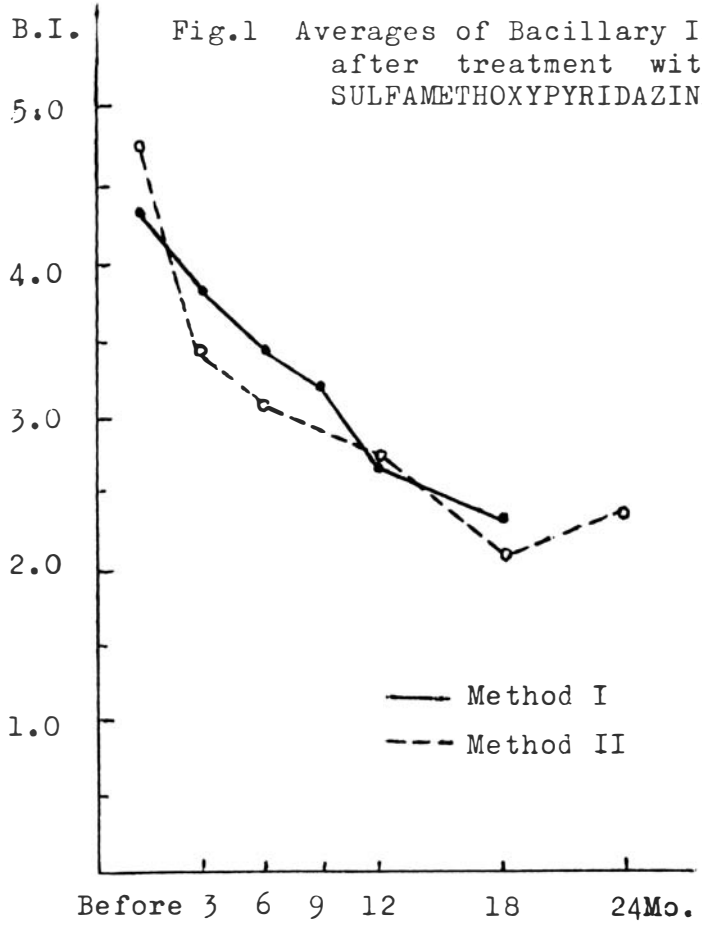
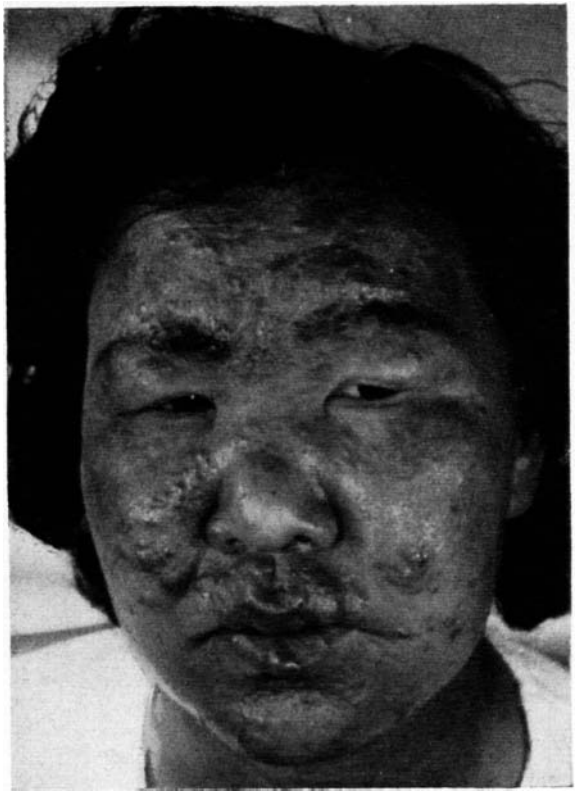


Fig.1 Averages of Bacillary Index after treatment with SULFAMETHOXYPYRIDAZINE

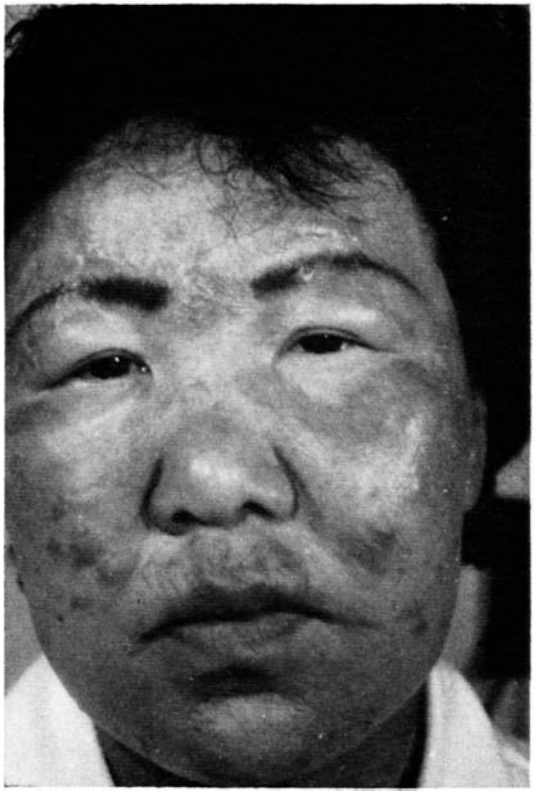
Epithelioid cell reaction in lepromatous leprosy derives from two causes. One is Acute Infiltration Tajiri, due to relapse of the diseases. These patients, after years of treatment, develop a raised individual resistance to leprosy bacilli and the strong resistance thus acquired,

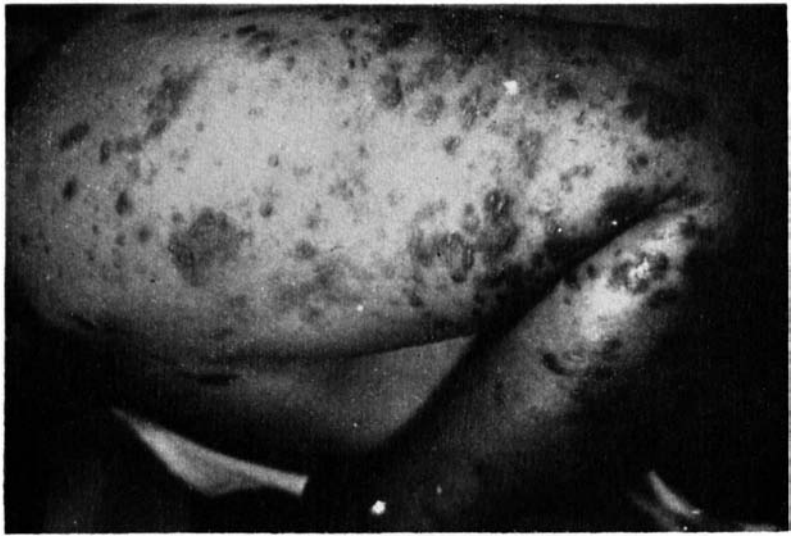
Case 1. New lepromatous case. 32 years old,

Before the treatment.

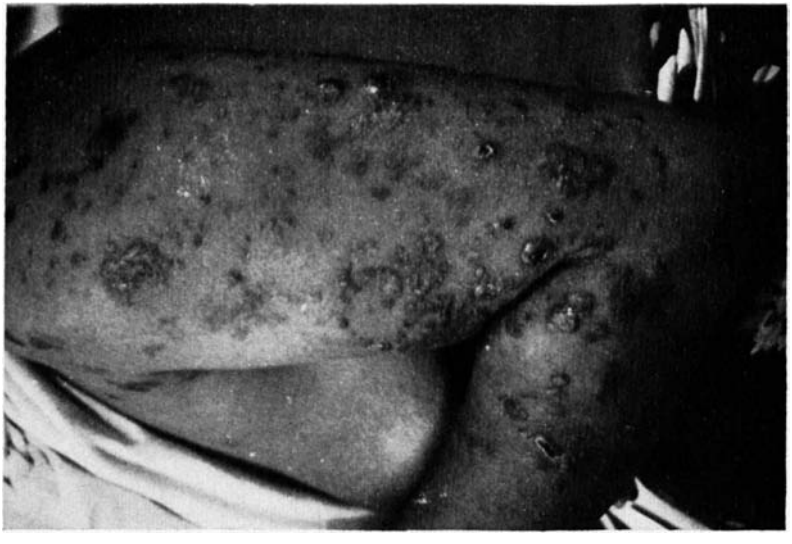


3 Mo. after the treatment.





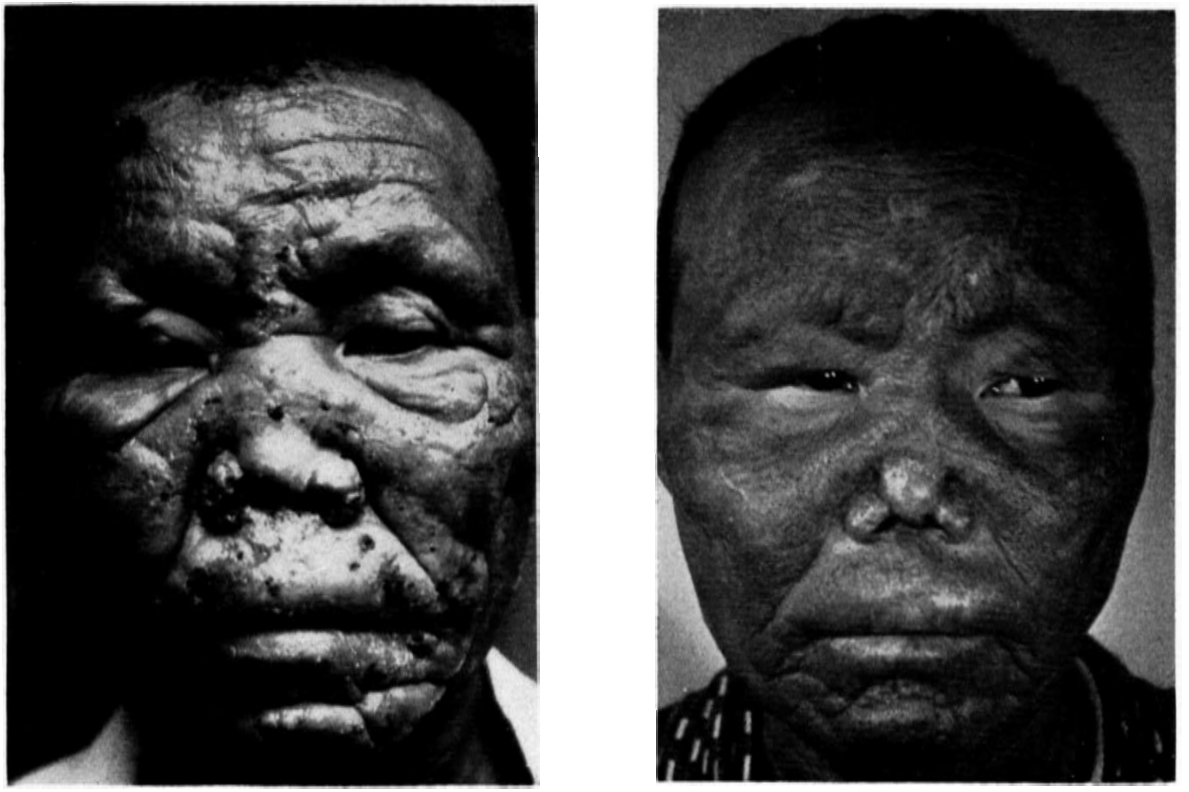
3 Mo. after the treatment.



Before the treatment.

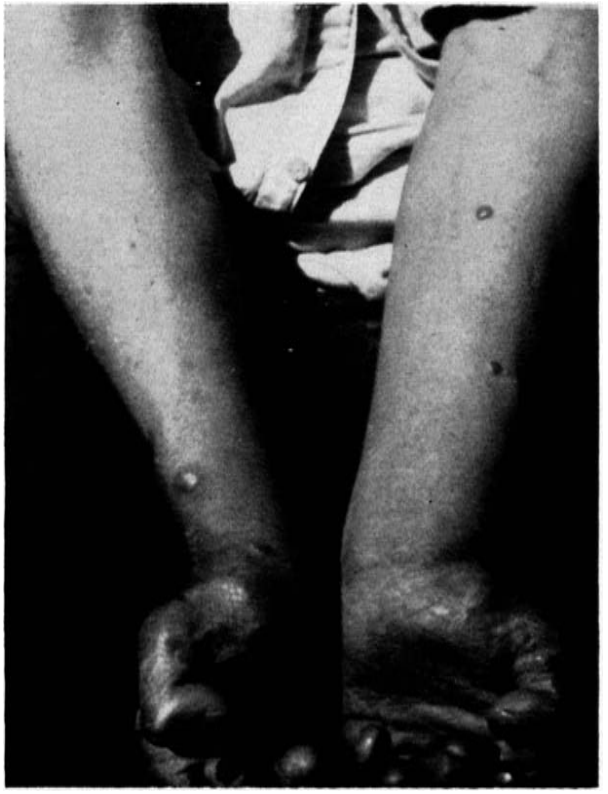
Case 2. New lepromatous case. 35 years old,

Before the treatment *One year after the treatment*

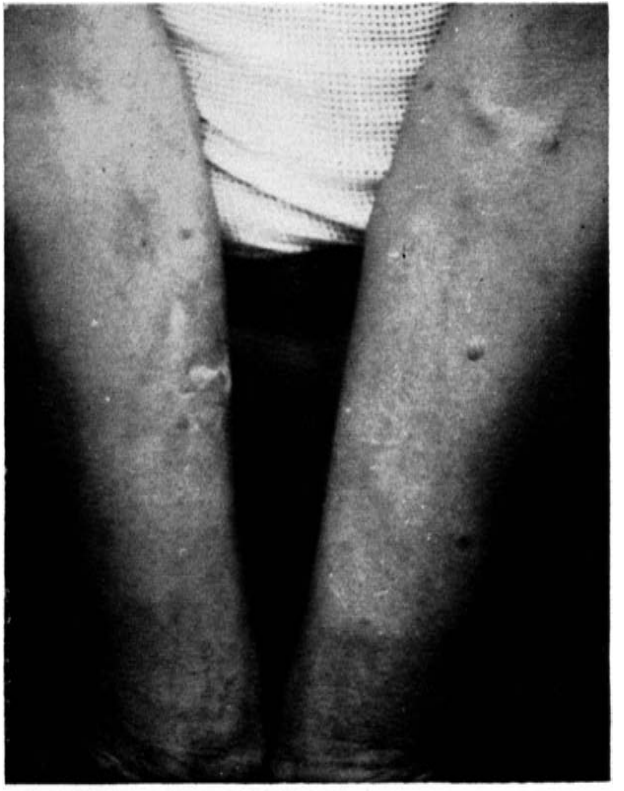


Case 3. Relapsing and DDS & CIBA 1906—resistant lepromatous case. 34 years old,

Before the treatment

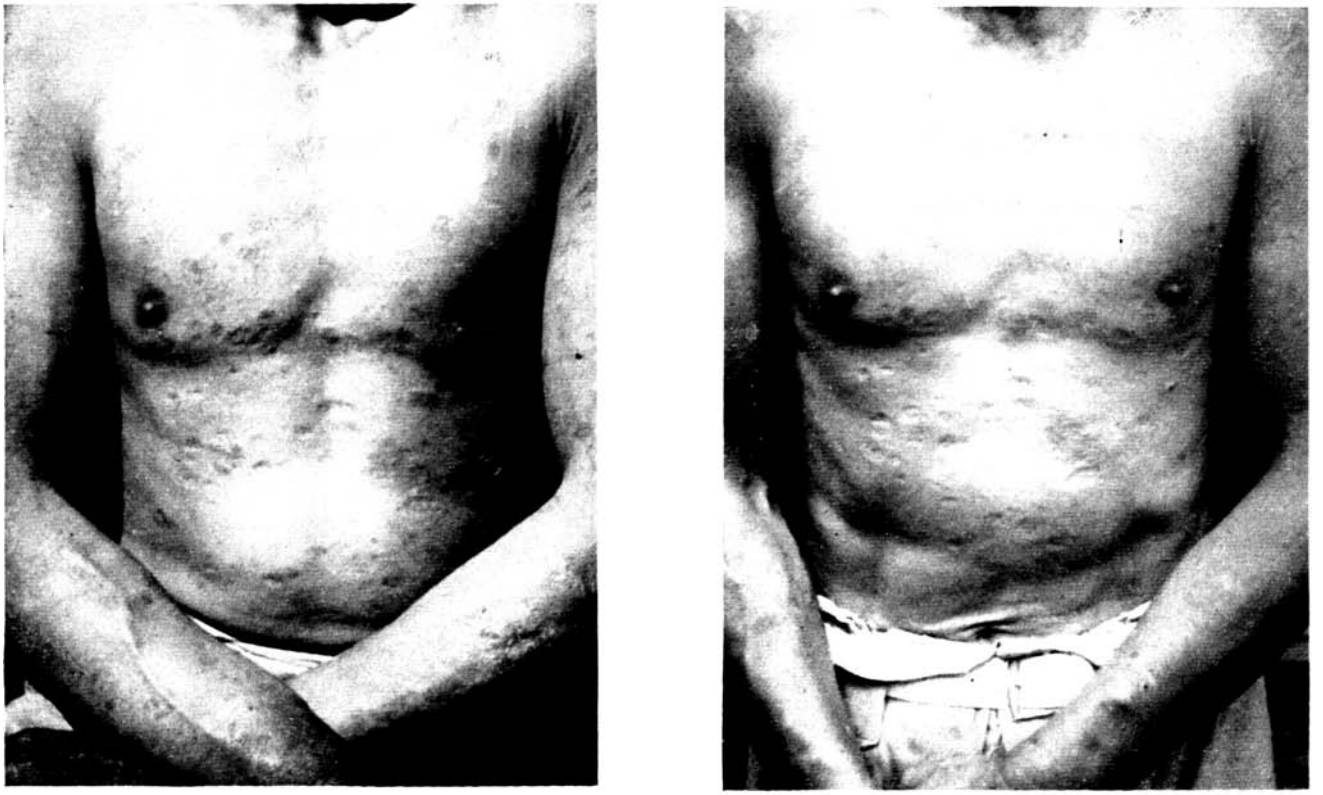


4 Mo. after the treatment



Case 4. Relapsing and DDS and CIBA 1906—Resistant lepromatous case.

Before the treatment *After the treatment*



expressed itself as relapse with tuberculoid response. Since the use of chaulmoogra oil many years ago in Japan, several patients with the epithelioid cell reaction occurred and such causes have occurred every year. Since the common use of chemotherapy, the occurrence of such cases, as mentioned above, has increased, only a little, but still amounts to only a small proportion of the total number of cases.

This type of reaction, we shall call 'Secondary lepromatous improvement' since the pathologic improvement occurs as secondary to relapse of the disease.

Another substantial form of improved reaction 'Pseudo-exacerbation de Souza Lima' has been observed only after the common use of chemotherapy. This type of reaction is seen within one year after the treatment. Cases with this type of reaction (improvement) have gradually increased due to early diagnosis and intensive treatment.

The latter type of improvement is designated as 'Primary lepromatous improvement', since this forms the substantial improvement of the pathological condition. And both types together, we shall call 'Epithelioid cell reaction in lepromatous leprosy'. Incidentally, these natures are the same as tuberculoid leprosy. The occurrence of the epithelioid cell reaction in the form of Pseudo-exacerbation of lepromatous leprosy dates back to the initial clinical applications of sulphone drugs.

It is experimentally believed that sulphone drugs cause a strong activation of reticuloendothelial stimulation. Therefore, we believe this is the reason for the occurrence of this phenomenon. On the other hand, it is common knowledge that thiourea preparations produce a few reactive inflammations. In more than 100 cases given thiourea preparations in our leprosarium, the development of epithelioid cell reaction has not been observed in any of the cases, but in those cases using sulphone drugs this reaction occurs very often. It is believed that sulphone drugs cause a strong activation of the reticuloendothelial system, and Sulfamethoxypyridazine is able to remain long time in effective blood levels, consequently developing stronger and longer action on the R.E.S. than sulphonamide such as DDS or Promine, etc. In fact, the occurrence of epithelioid cell reaction was observed in 9 cases out of 100 cases given these drugs (about 10%). Hence, sulfamethoxypyridazine may be regarded as very useful for the complete cure of leprosy and for shortening the period of treatment.

Summary

Sulfamethoxypyridazine has been used for drug-resistant, relapsing cases and for new cases making a total of about 100 lepromatous cases. This drug was effective in both new and old cases and had no particular side effect within the 24 months when

observations have been done. During the treatment with sulphone drugs, Epithelioid cell reaction or so called Pseudoexacerbation de Souza Lima was observed. When this reaction occurs in lepromatous cases, all clinical findings became similar to those of tuberculoid cases and the bacilli also became negative soon.

So we consider that it is necessary for the treatment of chronic inflammatory diseases such as tuberculosis or leprosy, etc., not only to receive a specific drug but also to utilize this biological action.

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ANTITHYROID SUBSTANCE AND LEPROSY

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The theory behind the use of antithyroid substances in the treatment of leprosy was originally presented in 1957 by Dr. ARTURO O'BYRNE in a preliminary note to a meeting of directors of dispensaries and leprosaria of the Republic of Colombia. Later, in May 1958 Dr. O'BYRNE presented his thesis before the First National Congress of Leprology in the city of Cartagena, Colombia.

The importance of this theme is undoubted. I believe that the theory of the importance of iodine in relation to the bacteria will be of great assistance in solving the problem of rational therapeutics of leprosy.

One of the basic postulates which have to be investigated fully is that of seeking and finding existing analogies between known antithyroid drugs and leprostatic drugs; for the chemical, biochemical, and physiological relationships of the compounds in question show us that the basis of their action can be expressed as hypoiodaemic action affecting the thyroid gland directly, and indirectly the tissue iodine.

As a confirmed fact we know that the iodine of iodine compounds is very harmful to the leprosy patient. As A. O'BYRNE says "The relatively simple consequence that a substance administered in the course of an infectious disease is harmful to the patient and causes the multiplication of the infecting agent, derives from the fact that it enhances the vitality of the microbe at the expense of the life of the patient."

In future investigations we should take into account whether we should think of the leprosy patient more as an hyperiodaemic than as a hyperthyroid.

If the increase of iodine in the blood causes exacerbation of the lepromatous lesions, diminution of iodine in the blood can provoke a regression of the disease.

Up to this day leprosy lacks a specific and rapidly acting curative medicament, and this has not been due to lack of experimentation but to lack of exact knowledge about the pathogenesis, that is to say, we lack a 'biological model', for reasons known to all. Because we do not have this biological model in animal experimentation, the difficult therapeutic problem in leprosy must be studied directly in patients. So it is that in leprosy a logical lack of confidence exists in every new treatment which tries to rise.

Antithyroid drugs present as possibilities in the treatment of leprosy because of existing analogies between iodine on one hand, and the thyroid gland on the other, also between tissue iodine and the harmfulness of iodine, as much for tuberculosis as leprosy patients.

The antithyroid substances are the most powerful antioxidants which can operate in the tissues; they operate through the medium of iodine and can change the background and make it favourable to the proliferation of the bacilli.

The thyroid gland has an enormous capacity to store iodine, up to 500 times more than any other body tissue.

In thyroid hyperactivity there is a diminution of thyroid iodine and an increase of blood iodine, both of which are signs of oversecretion of thyroxine. One can suppose an increase of tissue iodine.

The activity of the gland shows many variations. For example it decreases during old age, under raised temperatures, during chronic diseases, and as a result of toxic influences, etc. It increases through seasonal fluctuations, during adolescence, during childbirth, through emotional trauma, during the menopause, etc.

The leprosy patient undergoes frequent reactions in his disease, and these reactivations coincide, and not by mere chance with periods of thyroid hyperactivity. We have observed these outbreaks and leprosy reactions during the premenstrual epoch, during childbirth, in adolescence, in seasonal changes and even very often during emotional upsets, and we have seen their attenuation and the development of benign forms of leprosy in old age, when they are accompanied by other chronic diseases, or when there is a change caused by toxic influences.

One wonders if the leprosy patient could arrive at the stage of being considered as an atypical form of hyperiodaemic hyperthyroidism?

Various atypical forms of hyperthyroidism coincide with the initial typical forms suffered by most leprosy patients, namely the dyschromic forms (whether hyperchromic, acromic, or hypochromic); profuse sweating; amyotrophy and swellings of the limbs; neuritis and polyneuritis; muscular asthenia and functional impotence; impaired nutrition; hepatic insufficiency; hepatic lesions; psychophysical instability; changes in the mucosae, such as rhinitis; etc.

If we admit that the leprosy patient is a hyperiodaemic hyperthyroid, it can be expected that as a consequence of antithyroid treatment the stability of the thyroid gland is only attained after several months and even years, but this does not include the fact that the iodine concentration in the tissues and in the circulation may fall in a relatively short period of time.

The antithyroid substances work rapidly and surprisingly. After 6 to 8 months the therapeutic progress is relatively slow. This may be explained because the antithyroid drugs at present in use work more on the thyroid gland than on the tissue iodine, that is to say they impede the transport of glandular iodine to the tissues.

The rapid initial improvement is explained by the decrease of the iodine in the blood and in the tissues.

ROSALINE PITT-RIVERS says "Possibly the human being as well as experimental animals may respond to a physical or emotional stress by an increased activity of the suprarenal cortex. In the same way if for any reason the suprarenal cortex fails in its response and hence if the inhibitory effect of the corticosteroids on the production of thyrotropine does not present, a thyroid hyperactivity is produced." We add that thyroid hyperactivity would aggravate the evolution of leprosy, and so we have found in our experience.

In this connection we should remember that Dr. OBERDÖRFER proposed the use of diphtheria toxoid as a protection for the suprarenal gland, basing this on his theory of suprarenal insufficiency in leprosy patients due to dietary consumption of sapotoxins.

Taking into account what has been said we should perhaps interpret the N Factor of ROTBERG as a constitutional variation in the iodine content of the tissues. Hence we can say that human beings lacking the factor of resistance would form a group with too much iodine in the blood, or the Mitsuda-negative patients. On the other hand the human group which possesses the factor of resistance would be Mitsuda-positive and possess too little iodine in the blood. A third group can be separated out, namely the 'indeterminate', which fluctuate from one to the other. This group would coincide or be the analogy of the 'overlapping group' as described by ASTWOOD and CASSIDY, that is patients who cannot be exactly described as hyperthyroid or hypothyroid.

In our experience the lepromatous leprosy patient is able to take many times more than the maximum therapeutic dose usable in the hyperthyroid patients. Therefore it is advised to begin the treatment with dosage not less than 40 mgm. daily of methimazole or 120 mgm. daily of propyl-thiouracil, until in a few days the progressive dosage is reached which fits the reactions and the development of each patient.

The fear of hypothyroidism is or should be very remote and up to now has not intruded itself except in a very small number of patients. To meet this threat it suffices to suspend the treatment for a necessary time.

In my opinion it is advisable, after 6 to 8 months of treatment by methimazole or by propyl-thiouracil, to use a modern antileprosy drug such as DDS in dosage of 25 to 50 mgm. daily.

We should pay attention to the fact that DDS has an undoubtedly antithyroid chemical structure.

The initial violet or erythematous colour of the lepromatous lesions is changed by the treatment into a brownish colour and later takes on a pigmented melanotic tint, remaining thus for an indefinite period of time. The pigmented melanotic tint increases on continuing

the treatment by antithyroid drugs of the methimazole type. In some persons the melanotic tint decreases if the antithyroid drug dosage is reduced. In other persons there is a new change to a pigmented erythematous tint when the drug is suspended or changed.

Not all leprosy patients are suitable for the antithyroid treatment, but those who benefit most from the use of these drugs are those in whom greatest malignity exists, namely those with diffuse infiltrations, lymphangitis, frequent lepra reactions, papulo-mucosal lesions, also reactional tuberculoid cases, and those with localized signs of obstructive rhinitis, or polyneuritis, or lepromatous patients with hyperaesthesia.

The antithyroid drugs are of very little use in patients who have been treated extensively with other leprostatic drugs and in those very extensively nodular. It is possible that in these latter patients there should first be application of physiotherapy.

As a 'note in the margin' we should like to point out the antithyroid chemical constitution of Ciba-1906.

The improvement obtained with the antithyroid drugs in leprosy cannot yet be claimed to be permanent, due to the short period of experimentation so far. The questions arising in connection with this new theory are so numerous and the facilities for solving them so few.

From personal communications from Dr. O'BYRNE in recent months it can be said that modifications and progress have been made in the use of antithyroid drugs in the treatment of leprosy. I consider these modifications logical and am in accord with them, as follows:

1. The dosage of methimazole has fluctuated around 100 mgm. daily, and of propyl-thiouracil around 500 mgm. daily.

2. The therapy of these substances has become associated with what Dr. O'BYRNE calls the 'antithyroid diet', namely a dietary regime in which salt-free iodine is used, an abundance of vegetables of the Brassicae or Crucifera type, a scantiness or suppression of foods too rich in the amino-acid tyrosine, foods which could influence the organic deposition of iodine, the preferential use of poly-desaturated vegetable oils (which have been recognized for a long time as antithyroid).

3. Relative decrease of carbohydrates in the diet and progressive increase in the proteins and in the polysaturated fatty acids.

4. Prohibition of fish and every food of marine origin.

5. The prudent use of wine is advised, or of glucose, in its role as reducing substance.

6. In some cases there has been added to the methimazole or the propyl-thiouracil a solution of sodium thiocyanate in drops up to a

dose of 300 to 400 mgm. daily. This association has the special object to speed up the elimination of iodides by the kidneys in accordance with the observations made by VAN DER LAAN.

7. With the object of decreasing the tissue iodine in lepromatous patients one can equally use the capture of the iodides in the gastro-intestinal canal.

We know that the iodine ion eliminated through the gastric juice, the bile, or the other intestinal juices, is absorbed again with great speed and efficiency by the intestine, in such a way that the loss of iodine ion by the intestinal route or foecal route is insignificant. If we administer classic antithyroid drugs to a lepromatous patient, these substances produce the inhibition of the synthesis of the thyroid hormone, that is, interfere with the incorporation of inorganic iodine within the prehormonal organic compounds. Hence we can accept that as a first consequence of the administration of antithyroid substances, there is an increase of the elimination of the iodine ion by the biliary and gastric tract, since the said iodine ion has failed to be used in the making of thyroid hormones.

If simultaneously with the methimazole or with the propyl-thiouracil we administer a substance which can trap the iodine ion in the intestine, a substance which at the same time would not be absorbable by the intestinal mucosa, we will have succeeded in increasing the elimination of iodine by the foecal route.

The substances which are met with at the present time in experimentation associated with methimazole or propyl-thiouracil are succinyl sulphathiazole and sulphaguanidine.

Some lepromatous leprosy patients treated with these modifications in recent months have obtained appreciable improvement compared with that obtained with the exclusive use of methimazole or propyl-thiouracil.

8. A new path of investigation in order to confirm the possibilities of this theory is *quantitative analysis of iodine in the skin* of leprotmaous leprosy patients. Such an analysis would be compared with the skin of patients free of leprosy resident in several countries of the world.

Summary

The logical treatment of leprosy should be related to the iodine metabolism.

The basis of action of antileprosy drugs is the hypoiodaemic concept. To acquire or not acquire leprosy depends on the greater or less proportion of circulating iodine or tissue iodine. The dosage of antithyroid drugs administered to leprosy patients should be greater than that given to hyperthyroid patients. It has been shown that they are well tolerated.

Not all leprosy patients respond to the action of the antithyroid drugs, just as not all have the same iodine proportion.

The quantitative analysis of skin iodine in patients of lepromatous leprosy cannot be dispensed with.

Acknowledgements

I have to thank Dr. JAMES ROSS INNES for his kindness not only in translating this paper into English, but also for publishing it in *Leprosy Review*.

I thank Dr. ARTURO O'BYRNE for permission to explain some of his ideas on which I have been in constant consultation with him. The collaboration of his indomitable spirit which ever seeks perfection has been much appreciated, also his brotherly friendliness.

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A PRELIMINARY STUDY OF THE THERAPEUTIC EFFECTS OF 'VADRINE' IN LEPROSY

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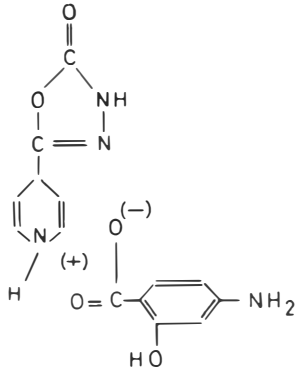
Vadrine is a new Anti-Leprosy drug with the chemical name of 2-PYRIDYL-(4)-1,3,4-OXDIAZOLON-(5) p-AMINO-SALICYLATE, the following chemical formula:



2-Pyridyl-(4)-1,3,4-oxdiazolone-(5)-p-aminosalicylate

Its tuberculostataic activity was tested by BRODHAGE and SMITH as early as July, 1955 *in vitro* and *in vivo* and was found to be equal to that INH with much lower toxicity in guinea pig tests.

It has been tried as well reported on from Britain and from Rhodesia by JOPLING and RIDLEY and ALLAN. In another report BRECHET says that Vadrine has advantages in its rapid action in the first 12 to 18 months, its lack of toxicity and side effects and its reactions are at a minimum; when tried alone it was found to develop drug resistance after about a year by JOPLING. BRODHAGE has tested this drug on animals, particularly rats, along with DDS on murine leprosy, experimentally introduced into the testes. He has reported that both the drugs singly have very little effect on the bacilli, while together they inhibit the increase of mycobacteria to a marked degree. In murine leprosy, he says, Vadrine is superior to DDS.

As far as is known this drug has not been tried in India. Ten thousand tablets of 400 mgm. each of Vadrine were placed at our disposal by Ed. Geistlich Sons, Chemical Works, Switzerland, for trial at this leprosarium in May last year. It was decided to try its effects on patients having nasal, ocular and laryngeal lesions in conjunction with the usual dosage of 600 mgm. per week of DDS. The dosage selected for this preliminary report of Vadrine was

10 mgm. per kg. of body weight three times a day, i.e. 30 mgm. per kg. of body weight daily.

This treatment was started on 11 patients after complete examination of nose, eyes and larynx and also general examination to exclude any other disease accompanying leprosy. The treatment was continued for 3 months.

No controls were studied as these patients had been steadily getting worse in spite of the full dosage of DDS for the last 6 months and nothing else did any good to their nasal, ocular and laryngeal leprosy.

The greatest effect of this three monthly experiment was seen in nasal leprosy, the results of which were recorded in 11 patients as 'good' or 'very good', both clinically or bacterially; the bacterial index was negative in 1 case in the nose, and 1 or less than 1 in all others, after an initial bacterial index in the nose of 6, 5 or 4.

Very little effect was seen on ocular and laryngeal leprosy. At the end of three months the nasal smears were again taken and showed a marked improvement in bacillary index. The bacilli in most of the cases appeared in broken forms which are considered to be non viable bacilli according to the latest view. In some cases the nose became free of leprosy bacilli, which considering the fact that generally it is the last part to be free, is remarkable.

In the natural progress of the disease in the nose, the first microscopic change noticed is the general swelling of the cartilaginous parts. In this series case No. 6 Shri Guru Pado was a patient of this type. His nose became free of leprosy bacilli at the end of 3 months and the swelling disappeared leaving no deformity at all, thus avoiding the ugly deformed nose which would have appeared in the ordinary course of leprosy treatment with DDS.

No resistance to the drug developed during this period in any patient. It is proposed to restart the treatment after a rest period of 2 months.

Reactions

Reaction appeared in 4 cases out of 11 ranging from mild itching on the face and other parts of the body to severe erythema nodosum leprosum, high fever, inflammation of the lepromatous lesions, and ulceration. Only in one case No. 10, which was severe, was the treatment stopped. In this case treatment had to be stopped completely not only with Vadrine but also with DDS. The reaction came on the 51st day of the treatment. The reaction was brought under control after 18 days but Vadrine was not given again because of fear of bringing on another reaction. The patient was put on hydnocarpus oil injections. The nose condition in this case became worse and the bacterial index during the reaction increased but at the end of the reaction it decreased markedly again. In the other cases

the ulceration of the nose responded by slight improvement to complete healing. The cases which had already developed nose deformity had symptoms connected with the deformity, and did not improve and required surgical treatment.

Other cases of ulcers which were positive for leprosy bacilli were also improved and the ulcers healed. There was no effect on trophic ulcers infected with secondary organisms.

Summary

Vadrine 30 mgm. per kg. per day with 600 mgm. weekly of DDS was tried on 11 patients having nasal, ocular and laryngeal complications for 3 months. The drug had a very good effect on the whole on nasal complications, but slight or no effect on other complications.

Severe reaction was noted only in one case out of eleven.

Conclusion

Vadrine in conjunction with the usual dosage of DDS has an accelerating effect and makes the patients free from *Mycobacterium leprae*, especially in the nose, during the first three months of treatment.

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EXPERIMENTS IN THE TREATMENT OF LEPROSY WITH ETOXID (PRELIMINARY INFORMATION)

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Translation by the kindness of Dr. J. I. MIRILOW.
(From the article published in Ucheniye Zapiski 3 (8) Astrakhan 1962)

Recently information has appeared in literature (scientific literature) about the effectiveness in treatment of leprosy with a drug manufactured by CIBA-1906 or DPT. (INNES *et al.* 1957, DAVEY 1958, GATE 1958, DOULL 1960, DAVEY 1960, NAZAROV 1960). This was synthesized by American research workers HUEBNER *et al.* and made possible to be put on the market by the CIBA research workers. This drug proved to be effective in the treatment of tuberculosis *in vivo* as well as *in vitro*.

Compound 1906 was put on the market by a Swiss firm of CIBA and is composed of p-butoxy p-dimethylaminothiocarbanilide.

In the past year a number of medical preparations have emerged the present one being a derivative of diphenyl-thiourea which was recommended for the treatment of T.B. and leprosy.

In 1953 in the laboratories of Professor M. N. SHUKIN (The Institute for Scientific Research in Chemistry and Pharmacology of the U.S.S.R.) a compound was synthesized belonging to the group of thiocarbanilides, namely Etoxid which is in itself diethoxy-thiocarbanilide.

This is a white or slightly yellowish crystalline powder, bitter in taste, and it melts at a temperature of between 168-271°C. It is insoluble in water, ether and chloroform but is soluble in acetone and alcohol. This preparation possesses a high bacteriological activity and has been selected with respect to bacteriocidal action on the mycobacterium of tuberculosis.

Growth of other pathogenic bacteria has been suppressed. A detailed publication about this synthesis was completed in 1960 by N. B. GALSTUKHOVA and M. N. SHUKINA.

In our national literature we have a large amount of information about the effect in treatment of tuberculosis with Etoxid.

A. KAMINSKAYA and E. Z. MIRZOYAN (1959) administered this drug to 48 patients with rather old and diffused pulmonary process. This was actually the introduction of the drug in the treatment of tuberculosis when certain other chemotherapeutic drugs had failed. Favourable progress was noted in 15 patients after X-rays were taken at the time of treatment and during a period of between 1½-2 months.

The drug acted effectively. In some of those patients it appeared to have decreased the catarrh and there was marked normalization in haemoglobin but less marked normalization of the leucocytosis. An increase in the number of lymphocytes was also noted.

N. A. SMELEV (1960) noticed that application of Etoxid in the treatment of tuberculosis during the course of illness was well tolerated. Etoxid is the only one that does not combine with any other anti-tuberculosis drug and can bring about a process of resorption of the peripheral infiltrations (in leprosy).

G. N. PERSHIN and T. N. ZIKOVA (1961) noticed the effectiveness of Etoxid as an anti-tuberculosis drug which exercised an anti-bacterial effect on *Mycobacterium tuberculosis in vitro* as well as in chemotherapeutic effects in the course of the experiments, for example in tuberculosis with white mice and guinea pigs. Etoxid possessed a therapeutic effect in patients suffering from different types of tuberculosis. At the same time the best results were achieved with Etoxid during the treatment of fresh cases of tuberculosis. Authors have recommended Etoxid as a drug for the treatment of tuberculosis where there was a positive presence of tubercle bacilli and stability towards streptomycin and pthivazid, etc.

M. N. SHUKINA (1961) has proved, by gathering all evidence she obtained during the *clinical trials*, that the drug possesses good therapeutic properties for the treatment of tuberculosis. Her information enabled us to pass that information on for the use of Etoxid on a wider basis. We also have clinical evidence which we obtained by testing that drug in connection with the treatment of leprosy. We have had under our care 24 male lepromatous patients, 11 male tuberculoid leprosy patients and another 11 male patients with the undifferentiated type of leprosy. There were 8 men and 16 women patients. In the age group up to 20 there was one male patient; in the age group 20 to 30, 4 male patients; in the age group 31 to 40, 1 male patient; in the age group 41 to 50, 7 male patients; in the age group 50 to 60, 5 male patients and over the age of 60, 6 male patients.

During their illness they were classified in the following order. As far as the first year of treatment was concerned there were 4 male patients, between the first and the second year, 16 male patients and between 3 to 5 years 3 male patients and over 5 years one male

patient. Before the introduction of Etoxid the lesions on the surface of the skin of the above patients treated previously with anti-leprosy drugs did not heal but on introducing Etoxid the results were good. So we introduced Etoxid in the following order. In the first week at 0.1 g. t.d.s. In the second week the dose was increased to 0.2 g. t.d.s. and in the third and subsequent weeks 0.3 g. also t.d.s.

At the beginning of the twenty-first week all those patients who were isolated had shown good tolerance in respect of the drug and the daily dose was increased up to 1.5 g. That treatment was carried on for 40 weeks after which period followed a month of rest.

This course of treatment was administered to 15 male patients and the other patients were treated with Etoxid from between 4-8 months. In the group of patients who were affected with the lepromatous type of leprosy (11 male patients) there were characteristic infiltrative changes of varying degree. These infiltrative changes were manifested on the faces of these patients, on their extremities and in general on their bodies. In three of these patients nodules were dispersed on their bodies and all over their extremities. In the case of five men patients there was definite evidence of thickening of the ulnar nerves but we also had a case of one patient with a muscular atrophy and contraction in flexion of the thumbs on both hands. On histological examination of skin specimens taken from the affected parts there was a definite lepromatous structure of the infiltrations with an abundance of homogeneous leprosy bacilli. Tests in all these cases were negative.

There has been observed during treatment with Etoxid, which lasted between 14-21 weeks, a regression of the specific manifestations. Infiltrations were gradually reabsorbed and the colour became paler. On the other hand, some of these infiltrations disappeared and in place of them we observed spots. Later on the regressive changes became more and more noticeable; regression of infiltrations and nodules was complete, and the spots disappeared. Improvement was general, the patients felt much better, and they also gained between 2-9 kg. When biopsy was repeated on the diseased portions of skin in 8 patients, it was noted that the second biopsy revealed infiltrations of the lepromatous type of leprosy, the infiltrations became smaller, fibrous changes appeared in the dermis, mycobacteria were noticeably reduced in number, and the disease manifested itself in the form of spots.

CASE HISTORIES: General Notes

(*a*) In one particular case a woman patient (case history No. 2890) was admitted with an infiltration of lepromatous type which was replaced later on after weeks of treatment by an infiltration of a rather 'roundish' type but without any evidence of the presence of *Mycobacterium leprae*. At that stage of treatment the connective tissue in the skin formed and went on to healing. The bacterial index became normal in 3 cases which previously had a reduced bacterial index.

In the case of 3 patients (sixth, twentieth and thirty-second week of treatment) there was a manifestation of a nodular type of erythema in all three cases but

without an increase in temperature and without any deterioration in the general state of health, despite the erythema, treatment went on. The erythema complication gradually disappeared.

(*b*) In the case of patient E (case history No. 2932) during the course of treatment the presence was noted of elementary nodular erythema which appeared and disappeared periodically.

(*c*) In the case of patient P (case history No. 2963) we saw in the course of the second month of treatment that the lepromatous process did not react to the treatment as might have been expected. The lesions and the hyperpigmented spots acquired erythematous colouring and also showed up in new elements. The treatment was not discontinued. Soon after that the giving of the drug lesions in the form of erythema disappeared and the lepromatous process was healed in the normal course of regression treatment. Here are short notes (case histories) which may help.

Case No. 1. Female patient age 60 (case history No. 2939).

The patient was admitted to the Institute for the Study of Leprosy on the 21st February 1960, and diagnosed as having the lepromatous type of leprosy. On her arrival at the Institute there were diffused infiltrations on her face, especially on her ears and ear lobes. In the region of her forehead and eyebrows the infiltrations were much deeper, and the eyebrows were rather sparse. On the upper and lower extremities marked infiltrations were observed which in places merged so that they formed infiltrations of the entire face. On the chest infiltrations were seen to be diffused, and some had clearly defined borders. A similar rash was observed on the buttocks and in the region of the hips. Along the tibia there were also diffused infiltrations in the form of flowers. Ulnar nerves were thickened on both arms and proved painful to palpation. ESR was 44 mm. per hour. Lepromin tests were doubtful. Skin biopsy of the portions affected by leprosy showed numerous infiltrations of the lepromatous type with a great quantity of homogeneous leprosy bacilli. After eight weeks of treatment with Etoxid some of these infiltrations subsided and became paler, and after 20 weeks of treatment the appearance of reactionary elements showed in the form of erythemas of a nodular type on the upper as well as on the lower extremities but the treatment was not interrupted. Body temperature remained normal. The general condition did not worsen. After thirty weeks of treatment the nodular type of erythema disappeared. The infiltrative inflammatory process remained until the end of the first course of treatment. Later on the above mentioned manifestations on the surface of the skin regressed noticeably. Deeply marked infiltrations of the extremities and of the body remained there but became more superficial. The puffiness of the face disappeared and the patient gained 2 kg. in weight. Nasal smear on October 1960 pointed clearly to a case of the lepromatous type of leprosy, but by repeating the examination of the nasal smear we noted that the causative organisms had disappeared. ESR was reduced to 22 mm. per hour. By repeated histological examination of diseased portions of the skin we did not observe any characteristic regression of the lepromatous infiltrations, no more than it revealed any presence of the leprosy bacilli.

Case No. 2. Female patient age 68 (case history No. 2932).

The patient was admitted to the Institute for the Study of Leprosy on the 28th September 1960 with a lepromatous type of leprosy. At the time of her admission this patient's upper and lower extremities were diffusely infiltrated. There were prominent superficial infiltrations on the chest, back and the buttocks. The ulnar nerves were slightly thickened but painless on palpation. There was reduction of sensitivity on the lower extremities, especially in the lower third.

Bacterial Index was 2.3 and the lepromin test was negative. Biopsy of the skin revealed the presence of disease in the form of infiltrations of a lepromatous structure with homogeneous bacillary foci.

After twelve weeks of treatment there was a certain reaction of elements which showed erythema in the limbs. Fifteen weeks after commencement of treatment we observed thickening and pallor of the facial tissue due to infiltrations. The same thing was observed on the extremities. After completion of the full course of treatment there was a disappearance of infiltrations on the face as well as on the body and there was considerable regression. On the upper and lower extremities in the place of former infiltrations there were some marks left of hardly noticeable hyperpigmentation. The nodular erythema broke out and recurred sporadically for a certain period of time, almost throughout the whole course of treatment. Lepromin tests were negative. The bacterial index

was normal. As far as the blood is concerned, we observed a reduction in haemoglobin down to 9.4 g.%. The patient was treated with Vitamin B12 and the haemoglobin went up to 12.6 g.%. After histological examination was carried out on a portion of the diseased skin it was found that the lepromatous infiltrations regressed as well as the destructive changes of *Mycobacterium leprae.*

Case No. 3. Male patient age 52 (case history No. 2914).

This patient was admitted to the Institute for the Study of Leprosy on the 22nd July 1960 with diagnosis of a lepromatous type of leprosy. At the time of his admission there were infiltrations on his face, principally localized on the forehead and around the eyebrows. There were diffused and deep 'hilly' uneven infiltrations of the nose and the malar infiltrations were rather superficial and of a rosy red colour with a flowery pattern. On the superficial parts of the chest, back, buttocks and upper and lower extremities there were noticeable infiltrations with deep infiltrative marks and on the feet hyperkeratosis. On histological examination of affected portions of the patient's skin we found the presence of homogeneous leprosy bacilli and infiltrations of a lepromatous type.

The results of treatment with Etoxid were remarkable after only 15 weeks of treatment. After the course of treatment was completed the pronounced and deep infiltrative marks on the patient's face faded out and in their place was left only superficial infiltrations. On the upper and lower extremities the infiltrations disappeared as well as those on the rest of the body. No lepromatous reaction was noticed. The lepromin tests which were at first negative became slightly positive. This patient gained a total of 4 kg. during his stay at the Institute.

Histological examination of the diseased portions of the skin revealed characteristic regressive changes of the lepromatous infiltration with the presence of leprosy bacilli.

In the group of patients affected with the tuberculoid type of leprosy (11 male patients) in 10 cases specific manifestations appeared on the surface of the dermis in a rather surprising form of papular 'limited' infiltrations. On histological examination of diseased portions of the skin, in all these cases, there was definite evidence of disease and a loss of sensitivity in affected parts of the body. It was noted in six male patients, that thickening of ulnar nerves was prominent and there was loss of feeling in the area. Atrophy of the muscles and contraction on moving the thumbs was noticed in four men patients. Lepromin tests with different intensity were positive in all these cases. On histological examination of diseased portions of the skin there was definite proof that those patients suffered from typical infiltrations of the tuberculoid type of leprosy. Although in one case the clinical characteristics were pointing to the tuberculoid type of leprosy, it was found on histological examination of the diseased portion of skin that infiltration of the lepromatous type was present.

During treatment of the patients in the above-mentioned group we observed a relatively quick clinical effect in the majority of cases. In those cases which were isolated we found that regression took place after two to three weeks. The reduction of the extent of infiltrations was well manifested by pallor and limited infiltrations. Macules disappeared and became clearer and papules if present disappeared.

In three patients, in places where the tuberculoid type of leprosy was evident, the recovery took place also as in sensitivity of the affected parts. In no case did peripheral nerve damage increase. The treatment was tolerated extremely well and all patients gained about

1.6k g. On repeated histological examination of six of these patients it was found that infiltrative lesions of a tuberculoid type were replaced by infiltrations of the ordinary inflammatory type without any presence whatsoever of leprosy bacilli. Formation of fibrous tissue and connective skin tissue was also noted. In three patients lepromin tests which were originally slightly positive became fully positive.

In that particular group there were five patients where the regression of the lepromatous type of process was very distinctive and they were discharged from the Institute in order to follow up their treatment as outpatients.

Now we propose to illustrate with some notes from case histories some observations regarding the above mentioned patients.

1. **Patient K.,** 49 years of age (case history No. 2967) was admitted to the Institute for Study of Leprosy on 26.1.61 with tuberculoid type of leprosy. On his admission it was found that marks of different size were present with clearly cut borders. On his chest, back, upper and lower extremities we have noted some type of round whitish skin marks. We have also seen in all these above mentioned skin manifestations already described, a limited reduction in patient's sensitivity. Ulnar nerves were thickened. In the upper and lower extremities there was a disturbance of sensitivity of the polyneuritic type. There was also an atrophy of the palmar muscles and muscular atony as well as a contraction of the third, fourth, and the fifth digits of the right hand when moving the digits. Lepromin tests were positive. Histological examination showed infiltrations of tuberculoid type without presence of leprosy bacilli as a result of one course only of treatment with Etoxid. The skin manifestations regressed and left afterwards hardly noticeable hyperpigmentation and the signs of atrophy of the skin. Contraction of the third, fourth and fifth digits of the right hand was to some extent decreased. Lepromin tests remained positive.

2. **Woman Patient S.,** 65 years old (case history No. 2966) was admitted to the Institute for Study of Leprosy on 18.1.61 with widespread tuberculoid type of leprosy in an active stage. On the cheeks, ears, and the double chin, it was noticed that limited infiltrations were present in the shape of flowers with indistinct borders. There were on the body numerous papular lesions and on the extremities clear cut erythematous lesions. Superficial sensitivity of the rash was reduced. Peripheral nerve trunks were not thickened. Skin on the shins and the feet was dry and atrophic, and bacteriologically negative. Histologically infiltration was of tuberculoid type but without leprosy bacilli. Lepromin tests were slightly positive. Here are the results of one course of Etoxid treatment: namely regression of infiltrations of the affected parts and of the spotty rash, and in its place pale marks remained in a form of a flower.

On the histological examination of the skin, after a course of treatment with Etoxid, it was noticed that there was some infiltrations of ordinary inflammatory structure but without any evidence of the presence of leprosy bacilli. Lepromin tests remained positive. The patient was discharged in order to continue as an outpatient. Clinical manifestations of disease with undifferentiated leprosy (two patients only) were characterized by a multitude of hyperchromic and erythematous patches. In one case of a patient with such patches, a reduction or loss of sensation was noted. Peripheral nerve disease was not seen in a single case.

On histological examination of the portions of skin taken from diseased patients from different parts of the body, there was a definite presence of round foci of infiltration and leprosy bacilli were present in one case. In both the above mentioned cases, lepromin tests were slightly positive. After the treatment with Etoxid, a remarkable regression was noticed in both patients. In a case of one patient (case history No. 2996) lesions were hardly

noticeable. Some scars had disappeared completely. Results of regression in that particular case was astonishing right from the start of the first week of the treatment.

Here I shall give you some details from a case history of another patient:

A woman patient 28 years old (case history No. 2958). She was admitted to the Institute for Study of Leprosy on 22.11.60 with diagnosis of undifferentiated type of leprosy. There was an evidence of a multitude of different marks of hyperchromic type on the surface of the skin on the patient's back, the buttocks and the extremities. Sensitivity on the surface of the skin was maintained. There were no evidence of damage done to the peripheral nervous trunks. Lepromin test results were slightly positive. On histological examination of the portions of skin there were simply small foci of infiltration of banal inflammatory structure but *M. leprae* was present. After the usual treatment with Etoxid the hyperchromic scars completely disappeared.

Lepromin tests were strongly positive. On repeated histological examination small simple inflammatory type infiltrations were observed in the skin without the presence of leprosy bacilli.

Summary

In the Institute for the Study of Leprosy at Astrakhan the authors used in clinical trial a derivative of diphenylthiourea named Etoxid which is diethoxythiocarbanilide synthesized by M. N. SHUKIN. This compound was found to have a high bacteriocidal activity in tuberculosis and there are many reports in the Russian literature about its use in tuberculosis, e.g. A. KAMINSKAYA and E. Z. MIRZOYAN, N. A. SMELEV, G. N. PERSHIN and T. N. ZIKOVA, M. N. SHUKINA, etc. In leprosy patients the authors report the use of Etoxid in a few cases in some detail. In lepromatous, tuberculoid and undifferentiated leprosy their results give a strong suggestion of significant clinical, bacteriological, and immunological improvement in a relatively short period of time, such as 15 weeks. The leprosy patients under treatment with Etoxid were 24 lepromatous, 11 tuberculoid, and 11 undifferentiated. The drug was given in a dosage of 0.1 g. t.d.s. moving weekly until 0.3 g. t.d.s. was reached. At the twenty-first week the dose was increased to 1.5 g. and the treatment was carried on for 40 weeks followed by one month of rest.

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WANTED—A LEPROSY POLICY

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My visits to a number of treatment centres for leprosy in different countries during the past few years give me the impression that there is need for a redefinition of the purpose of treatment in leprosy. This is particularly true insofar as it applies to 'Settlements' or 'Leprosaria' where patients are fed, clothed and housed for long periods. In some cases, it is not clear what policy is being pursued, and questions do not always elicit a coherent answer.

Much of this confusion is due to the changing emphasis in leprosy treatment that results from new knowledge and understanding of the disease. A further cause is the fact that many leprosaria are supported by Missions or philanthropic institutions and have often grown up round the personality of one or more devoted workers whose personal inclinations may dominate any constructive policy. Furthermore, Missions in particular are not so committed to bodily healing as are purely medical institutions and are willing to keep patients because of the spiritual or educational benefit which it is hoped the patient may derive or because, for humanitarian reasons, it seems difficult to insist on a patient returning to his home community.

However, conversation with those responsible for the work at these centres reveals frequently a feeling of frustration and dissatisfaction with things as they are.

With these things in mind, an attempt is made here to outline a leprosy policy that meets not only the humanitarian and Christian principles that direct many such instructions, but also provides a medically sound basis for action, in any leprosy programme.

What is the Aim?

There are three major needs in the majority of countries where leprosy is a health problem. These are, first, *the control of early infection*; this is specially desirable as it is generally agreed that early effective treatment will avoid the great majority of disabilities and deformities due to leprosy and in general result in cure. Second, the restoration of those who are moderately handicapped or disabled; and third: the care of those who are too disabled to be rehabilitated and are in effect permanent cripples.

The planning of a coherent plan for all three needs is the responsibility of the Medical Service of the region concerned. An isolated 'Settlement' should be perfectly clear, by a conscious act of decision, which of these it is to meet.

The most satisfying policy is to choose one and do it as well as possible; the least satisfying and the most frustrating, is to attempt

all three with limited personnel and funds and end in a morass of medical ineffectiveness and financial embarrassment.

It is regretted that too many of the 'Settlements' visited by the writer belong to this last group.

How to Choose

The first emphasis is on the fact of choice. It is very unwise to have no policy and just drift into a given situation owing to confusion of ideas and the force of circumstances.

The choice should be conscious and definite. Little is gained by hesitating between two or three possibilities over a period of years. For this reason, it is usually wise for the decision to be taken by a group of people, who should include one representative of the Medical Service responsible for the overall planning for leprosy.

The group should include someone of long experience in the many claims of leprosy sufferers, and also representatives from existing leprosy treatment centres.

The major decision must then be taken whether to concentrate on the effective treatment of early cases; or the rehabilitation of the partly disabled; or the care of the totally disabled. The early treatment is the least costly and probably the most fruitful, but it entails frequent travelling and work in uncongenial circumstances.

The rehabilitation programme makes the greatest demands on staff, building and equipment but avoids a considerable waste of young life and is the most gratifying to the worker. The care of total cripples is a work of charity but is the most costly, and is difficult to carry out with efficiency and devotion.

The Facts to Consider

Modern studies of leprosy make it possible to lay down certain basic principles which should guide all planning. These include:

I. With modern therapy, leprosy is a non-fatal, self-healing, chronic, infectious disease.

Leprosy proceeds in general slowly and quietly, interrupted by bursts of activity, to its final eradication by the body processes.

The damage it may do to limbs and face during this period may be considerable and may leave the patient a cripple. A few cases may develop serious complications and a few appear to live with their leprosy as a source of contagion all their lives.

II. The control of infective cases and the eradication of leprosy do not comprise a practical aim for many.

Although the control of infective cases is the only way to eradicate the infection from a community, the discovery and isolation of a sufficient number of cases to alter the general risk of infection is not practicable for many at present, in most countries where leprosy is endemic. The difficulty of finding and of recognizing the infectious

dimorphous cases, the expense and personnel that would be necessary and the impossibility of isolating the many thousands that would be discovered have led to the abandonment of the ideal of 'isolating infective cases'. Also, experience in the similar condition of tuberculosis has cast doubt on the value of such isolation. In a well-known experiment at Madras it was found that the contact-rate of cases carefully isolated at considerable expense was little different from those left at home in their families and treated where they live.

The moral is that the proper treatment of infective cases is to find them, treat them at home and keep a careful watch on contacts. These latter will be immediately treated on the first sign of infection. Prophylactic sulphone therapy is not yet known to be of value.

III. There is little value in treating a patient with anti-leprosy drugs, if the leprosy has already died out spontaneously.

This rather obvious 'truth' is emphasized because of the number of cases that can often be seen in 'settlement' who come into this category. Anyone treating leprosy should be perfectly clear as to when a case of leprosy is 'active', 'quiescent', 'arrested' or 'cured'. These are states well-defined in current textbooks and should be scrupulously observed. Cases of 'burnt-out' leprosy should not be kept on unnecessary treatment in order to qualify for money for their upkeep from philanthropic or government agencies.

The present section describes briefly the possible policies that can be followed. It is better to do one well than two poorly or all three badly.

The Control of the Early Case

In the present state of knowledge, and in the circumstances of many countries where leprosy is a problem the control of the early cases is the most profitable and satisfying way of using a limited amount of money. The essentials of this method include:

(i) regular visits to the places where people live,

(ii) particular attention to the examination of the young,

(iii) careful examination of the body,

(iv) a treatment policy for early cases.

The need for visits at intervals of six months limits the area that can be properly supervised with the personnel and funds available, but such a policy can be expected to bring about a notable reduction in leprosy within 20 years. The frequency with which leprosy begins in the young means that the schools should be especially visited. The tendency of leprosy to appear first in special areas (e.g. buttocks) underlines the importance of proper examination of the patient and the microscope is an essential part of equipment if early bacillus-positive cases are to be recognized.

It must be decided what should be done with early cases. This is a personal decision, because there is not yet general agreement on how to treat the early tuberculoid case. Many untreated cases, if followed year by year, recover completely without treatment. The writer suggests that a register be kept of all early tuberculoid cases and that they be re-examined without treatment at more frequent intervals (e.g. every two months) to follow the development of the case.

If however the total number of cases is small, such cases may reasonably be given full treatment from the start.

All treatment which consists only of the giving of tablets should be undertaken at home, without interruption of the patient's normal occupation. Particular care should be taken to begin sulphone therapy with a carefully graded series of doses so as to avoid complications of early overtherapy.

The occasional occurrence of incidents that cannot be managed in the patient's home will make some type of temporary hospitalization necessary. The best place to do this is the local general hospital if the prejudice against leprosy among patients and medical staff is not great.

To bring such patients in to a central 'settlement' is expensive and entails the risk that the patient may not return home readily after treatment and that his family may not welcome him home again. It should be avoided if at all possible.

The Rehabilitation of the Partially Disabled

At the present moment it is fashionable to emphasize the value of rehabilitation in leprosy and its value is undoubted.

However, proper rehabilitation is of value after any chronic disease and many countries do not have the resources to undertake much rehabilitation at the present moment.

The objective is to rehabilitate leprosy patients in the same medical service that serves other paralytic conditions, such as poliomyelitis and traumatic lesions of limbs and spine. Until this is possible it is permissible to undertake special care for leprosy; but this must be recognized as a temporary measure and large sums of money should not be spent in buildings in remote areas that cannot be used profitably for other purposes. The experiences of western countries with tuberculosis sanatoria is a healthy reminder of what *not* to do at the present time. If rehabilitation is to be undertaken it should fulfil the following conditions:

(i) Rehabilitation must accompany control of the disease.

If there is no adequate control of the disease in a community then rehabilitation of a small number of cases has limited value and is ultimately frustrating.

(ii) Rehabilitation must include care of hands, feet and eyes simultaneously.

It is of little value to spend much time over hand repair if the patient is allowed to become steadily blind, or crippled in his feet. No care is properly undertaken that does not include regular inspection of hands, feet and eyes.

(iii) Rehabilitation is largely non-surgical.

The urge to achieve a spectacular surgical 'miracle' must be kept in control. Surgery has a definite (limited) place in a planned scheme of treatment. It has no place as an isolated tour-de-force, stimulated by the reading of a paper in a medical journal.

Non-surgical rehabilitation includes normal physical therapy exercises, movements and such helps as heat (waxbaths, etc.) or electrical stimulation of muscle. Because of the frequency of plantar ulceration, plaster therapy and a sandal-making department are essential. Limb-making enables more serious cases to be treated.

The training of the patient in the care of his anaesthetic limbs is an important part of therapy. It is the writer's experience that where a patient is unable or unwilling to understand how he damages himself and how to avoid further damage, it is better to abandon this patient and concentrate on the more co-operative and intelligent. It is common for women of low education to be particularly un-co-operative in this respect.

(iv) The 'surgery of repair' is a special technique.

The operations involve tendon transfers, skingrafting and such bone-interventions as arthrodesis. Apart from the necessary skill in what are essentially skilled procedures, the facilities for adequate surgical sterility in the operative field must be present. Infection that would pass unnoticed in abdominal or general surgery can wreck the delicate mechanisms of the hand and a partly paralysed hand is of more use to a patient than a hand completely crippled by ill-advised surgery. No one should attempt surgery of this kind who has not seen what is involved by experiene at a centre where these procedures are normally undertaken; he should have become competent not only in the procedures themselves but in the maintenance of sterile theatre technique and the associated physical methods of rehabilitation.

The Care of the Totally Disabled

No one can fail to be moved by the sight of patients totally disabled by destruction of hands, feet and eyes in leprosy.

Obviously, something should be done to help them. But the worst thing is to allow policy to be directed by emotion and not by intelligence. The following considerations must be borne in mind when such work is being considered:

(i) Some damage is irreparable.

A patient with practically no fingers, with grossly distorted feet and partially or totally blind is probably a complete loss from a

medical point of view. This does not at all detract from his value as an individual, but it is wise to accept what is medically inevitable. Usually his leprosy is 'burnt out' and further leprosy treatment is uncalled for. The treatment of these cases is a problem in social welfare and not in medical care. In a modern Welfare State, these patients will be helped but it is not wise to use any notable part of a limited medical budget to attempt what is medically impossible, if by so doing those who can be saved are deprived of treatment. This applies not only to the use of money but also to the use of personnel which is also limited in most places.

It is the opinion of the writer that it would advance the cause of leprosy treatment to separate these cases, mentally and physically, from other patients and consider them as a special non-medical problem.

(ii) Some damage which is 'irreparable' may be reparable with new techniques.

A good example of this is the patient with grossly damaged feet who may become rehabilitated when cheap and effective artificial limbs become available. Present developments, especially in plastics, make it possible that at any time now these useful appliances may become practicable and cheap and attention should be paid to journals that describe them. It is regrettable that professional appliance-makers tend to emphasize their elaborate (and expensive) products and do not pay sufficient attention to the provision of cheap efficient ones.

There are also many cases in which techniques exist but are not readily available, locally. A good example of this is the repair of the collapsed nose of leprosy which is a considerable handicap to a young patient, especially a girl. The plastic repair of this is, to a plastic surgeon, a fairly simple procedure. Unfortunately the great majority of patients needing this intervention are far from centres of specialists who can perform it. The damage is therefore irreparable in the circumstances.

(iii) Some patients do not want to be rehabilitated.

No one can be helped who does not want to be helped; and it is an unfortunate thing that many patients view the prospect of rehabilitation (and the possibility of being asked to return home) with positive fear. Anyone with experience in leprosy knows of patients who will purposely damage their hands or feet, or provoke a reaction by overdoses of sulphones so as to avoid being considered as suitable for return home.

The blame for this is partly on the community at home who may not welcome him, but a share must be taken by ourselves as medical men who have (albeit in all good faith) built up a tradition in which leprosy patients expect to be cared for till death.

It is human weakness to prefer to be fed, clothed and housed without personal trouble, than to have to get up and make an effort for these things. This is true whether a person is affected with leprosy or not. We must accept part of the blame for having encouraged this, and do what we can to reverse the process. The problem is often more psychological and spiritual than physical.

Summary

1. The need of a clear policy for treating leprosy is emphasized.

2. The main needs are for: the control and treatment of the early case, the rehabilitation of the partially disabled, and the care of the totally disabled.

3. These basic schemes are discussed and the importance of a clear and intelligent choice is underlined.

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THE DIAGNOSIS OF UVEITIS IN LEPROSY

by H. E. HOBBS, F.R.C.S.

The incidence of blindness among patients afflicted with leprosy is unknown. The frequency of ocular involvement is found to vary in the different forms of the disease, from country to country and between separate communities in them. Reliable statistics appear only from the larger modern leprosaria where facilities for diagnosis and treatment are adequate and the proportion of cases with ocular complications from such centres is seen to be a good deal lower than that found by many leprologists among isolated communities. The opinion of KIRWAN (1955) that, if the patient lives long enough and the disease persists, some form of ocular leprosy will eventually appear offers some explanation of these apparently conflicting views. Experience in a small leprosarium in England* can provide no figures likely to be applicable to the general problem of blindness from leprosy; but certain conclusions with regard to the diagnosis of the conditions leading to it may reliably be drawn from cases in all stages of the disease examined there over a period of ten years.

The ocular lesions chiefly concern the cornea and uveal tract. Their diagnosis presents peculiar problems and in the detection of the earliest stages that of uveitis—iritis, iridocyclitis—is probably the greater. At both sites the reactions of the eye to invasion by the leprosy bacillus appear to be diminished: pain is subdued through ocular anaesthesia from trigeminal involvement and the diagnostically-valuable injection of the outer eye is much less than would be expected in similar forms of disease produced by other organisms. Thus the onset of these conditions less readily attracts the attention of either patient or doctor and some degree of permanent visual loss has not infrequently occurred when the patient first presents for examination. In the case of the cornea, however, premonitory superficial keratitis may herald the onset of neuroparalytic keratitis and lagophthalmos gives warning of the further damage to be expected from the incomplete protection of the diseased cornea. The turbid aqueous humour which is the early sign of the common form of iritis, on the other hand, is visible only to instrumental inspection and signs which present to the naked eye are likely to be those of established complications. Treatment with atropine and cortisone drops from the moment of diagnosis is imperative and, if continued throughout the period of activity, can control the condition and prevent serious visual loss.

Chronic serous or plastic iritis is generally acknowledged by ophthalmologists familiar with leprotic lesions to be the commonest

* The Homes of St. Giles, East Hanningfield, Essex.

manifestation of uveal involvement. Its onset is insidious and its course relentless for long periods. Inflammatory exudate from the iris and ciliary body passes into the aqueous and from it discrete deposits later adhere to the posterior corneal surface as keratic precipitates ('K'P.') or to the anterior lens capsule. Posterior synechiae form slowly; but may eventually occlude the pupil and result in secondary glaucoma. Nutrition of the lens, bathed in the pathological aqueous, is impaired and opacification frequently ensues. Disorganization of the globe with the appearance of gross staphylomata and phthisis bulbi are terminal events when vision has become extinct.

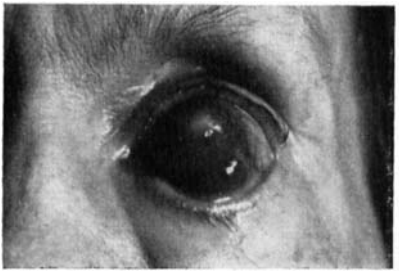

FIG. 1. *Patient H. B. Staphyloma following prolonged, untreated uveitis in arrested lepromatous leprosy. Vision: No perception of light.*

This sequence may also be seen following the appearance of 'iris pearls'—the deposits of lepra bacilli which so often seem to remain innocuous for long periods and which present one of the most fascinating pathological problems of the disease.

More rarely it begins with the appearance of leprosy nodules on the iris. The allergic type of serous iritis which is sometimes provoked in the course of the lepra reaction is more violent with more painful onset, greater ocular injection and a shorter, but no less visually-disastrous course.

Detection of inflammatory exudates in the aqueous calls for examination under magnification and critical illumination, i.e., with the light-source focused upon the object.

Such optical conditions are most accurately provided in the slit-lamp microscope, now considered an essential piece of equipment in every ophthalmic department. In its usual form it is, of course,

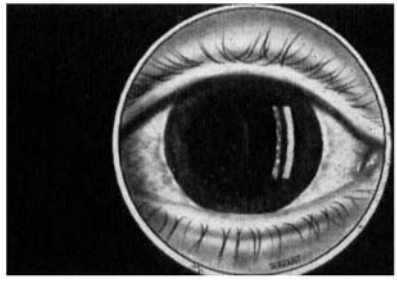

FIG. 2. *Aqueous flare and keratic precipitates in active iridocyclitis as seen in the beam of the slit-lamp microscope.*

static and thus accessible only to hospital patients. Professor Ida Mann's portable slit-lamp microscope offers a solution of this problem for the itinerant ophthalmologist; but it must be admitted that the biomicroscopic technique of co-ordination of illumination and microscope during the searching movements of both is an art not easily perfected by the occasional user of the instrument.

Similar, if less perfect, optical conditions may be produced with a loupe (x6 or x8) and a torch which projects the image of the lamp

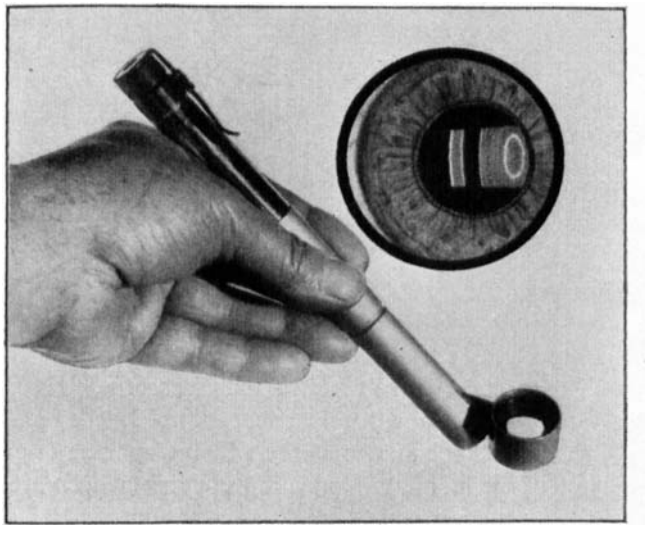

FIG. 3. *The ilmluinated loupe and (inset) the optical section of the cornea, lens and anterior chamber as seen with it.*

filament at its focus; but whilst these offer the desired degree of portability the bimanual technique of co-ordinating both whilst separating the eyelids with the fingers of one hand results in reliable

observations only after constant practice. In order to simplify this technique a battery-operated illuminated loupe has been made for me.*

In this the light from a linear-filament bulb is condensed to a line which coincides with the focus of a x6 loupe so that when the image of the eye under examination is brought into focus critical illumination is automatically achieved. As will be seen from the illustration this permits examination of a simple form of optical section of the transparent tissues of the anterior segment of the eye comparable with that of the slit-lamp microscope. The accuracy of this, as of that of any form of loupe examination, is, of course, considerably less than that of biomicroscopy proper; but the detection of a moderate degree of aqueous flare and of any but fine 'K.P.' is quite feasible with it.

This small instrument, originally designed for the purposes of undergraduate instruction, is inexpensive and simple in use, being easily held in the fingers of one hand whilst those of the other separate the eyelids of the eye under examination. It has proved sufficiently reliable for serious clinical use and may be found by the leprologist in the field a useful tool for examination of the anterior segment of the eye.

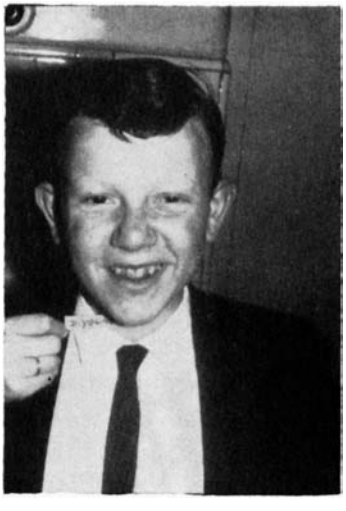

FIG. 4. *Patient D. Y. Active lepromatous leprosy of six years' duration responding poorly to treatment. Bilateral uveitis presenting as aqueous flare during the first year and controlled by continuous treatment with atropine/cortisone drops. Vision, after five years, 6/6, in each eye and reading comfortable with glasses.*

* By Stercks Martin, Ltd., New Cavendish Street, London, W.1. Price £4 17s. 6d.

Acknowledgements

I am grateful to Dr. R. G. COCHRANE who first suggested the publication of this note and under whose care, also, the patients illustrated are. Figure 4 is from his photograph and figures 2 and 3 were produced for me by Dr. PETER HANSELL of the Department of Medical Illustration at the Institute of Ophthalmology, London. The photograph in figure 1 was made by the Department of Medical Photography, The Royal Free Hospital, London.

Reference

KIRWAN, E. W. O'G.: *Proc. roy. Soc. Med.* (1955), **48**, 112.

ANNUAL REPORT—1962— OJI RIVER LEPROSARIUM

by Dr. W. F. ROSS,

Area Superintendent.

I. Introduction

(*a*) *General.* Our primary objective which is the eradication of leprosy from the Onitsha and Enugu Provinces remains unchanged, and some progress is being made towards this end. In general, the staff situation is satisfactory and financial position adequate; but, we continue to be handicapped by shortage of suitable Medical Officers for this work and limited funds in one key vote. (In particular, clinic tours have had to be seriously curtailed for several months and, at times, suspended altogether because of shortage of funds for transport, and of senior staff available for touring.)

(*b*) *Statistics.* It will be seen from our statistical returns that the number of lepromatous cases admitted this year, 56, as against last year, 31, has shown a considerable increase and has reversed the downward trend which we have seen in the last ten years. It is not possible to assess the true significance of this on the basis of one year's work only, but this trend is disturbing and confirms the need for continued vigilance in the leprosy service and for the maintenance of the service at full strength for some years to come.

(*c*) *Reconstructive surgery* has received considerable impetus this year by the regular weekly visits of members of the American orthopaedic team who come out here under the auspices of 'Medico Inc'. This work could now be considerably expanded, and more help given to patients from other Settlements if

(i) a second Medical Officer could be found to take responsibility for general medical and clinic work at Oji River, and

(ii) the diets vote could be augmented even more, to allow us to support more patients in the Hospital.

(*d*) *Prosthetics.* Through the work of Mr. Tom Forrest, two staff members have been trained in the production of artificial limbs. Thirty patients have been fitted with these limbs and we are satisfied that they are both practical and economical. We hope to be able to offer to make a limited number of limbs for amputees other than leprosy patients during the coming year and, perhaps, hold a course in limb making for folk from other institutions after the return of the Area Superintendent from his training in the U.S.A.

(*e*) *Footwear.* At the end of the year, the footwear workshop received very great stimulus and help from the visit of Mr. Turner, a Lancashire clog maker, who was able to help us with the design and production of footwear. During the year, 10 shoe makers from other Settlements have attended a 3 month's training course in this

Workshop. Both Mr. Turner and Mr. Forrest were financed by the British Leprosy Relief Association during their stay here.

(*f*) *Welfare.* The County Councils' welfare scheme continues to be the responsibility of the Welfare Department. Support has been increased in comparison with last year, but we have not been able to expand the scheme as much as we would like because of the very great and diverse responsibilities which the County Councils carry. There are still a number of disabled patients and ex-patients in need of help. The total number now being helped is 201.

(*g*) *Vocational Training.* Plans for the development of vocational training are also under the auspices of the Welfare Department and are going ahead. Mechanical engineering workshops have now been built and we expect the first trainees to begin soon. The Church Missionary Society have appointed an agricultural officer to work here in the Settlement and we hope to be able to announce shortly the beginning of a comprehensive programme of agricultural training, particularly, for deformed people.

(*h*) *Existing Medical Facilities for Non-Leprosy Cases.* We are still struggling along with the rather inadequate buildings for the large number of non-leprosy cases who now attend this institution. It will be seen from our statistics (C.M.F. 12) that over 16,418 out-patients attended this small unit and over 508 patients were admitted to the wards which normally hold 8 beds. The care and treatment of these large number of cases have only been possible because we have adopted the system recommended by Professor Bull in his report. The cases are all seen initially by an experienced Staff Nurse or Nursing Sister who then refers any which they cannot deal with to the Medical Officer. This system appears to us to be working very well and I would like to recommend it to other units who are overwhelmed with out-patients. It does, of course, place very considerable burden of responsibility on the Staff Nurses and we have been fortunate, so far, in having Staff Nurses and a Grade II Midwife of adequate quality for this work.

II. Administration

A. DEPARTMENTAL ORGANISATION. Not applicable.

B. STAFF :

(i) *Senior Staff*:

(*a*) *Medical Officers.* I said last year that I hoped it would prove possible to recognize leprosy as a speciality and create a specialist leprologist vacancy at the Settlement as I felt this would prove some incentive for an indigenous Medical Officer to specialize in this branch of medicine. I still think that this could be the solution of our chronic staff shortages.

(*b*) *Administrative Staff.* For nearly four months, no administrative officer was available for the Settlement. This inevi-

tably meant some loss of efficiency and some waste of our resources.

(ii) *Junior Staff*:

(*a*) *Clerical Staff*. We have now had practically a complete change of clerical staff in the past two years. It is inevitable that new staff take some time to work into the routine of the institution and such wholesale changes are not desirable. In addition, the quality of some of the new-comers leave a good deal to be desired.

(*b*) *Nursing*. We are glad that our junior nursing staff has been augmented by the appointment of 12 dressers. The quality of the applicants for these posts was very high indeed and, so far, we are very pleased with the work these young people are doing.

C. LEGISLATION. Not applicable.

D. FINANCE:

(i) I would again like to ask if it would not be possible to provide a contingencies vote.

(ii) Allocation of funds has been on a hand to mouth basis this year. It would make planning much easier for us and lead to more efficient use of available funds if we could be informed at the beginning of the financial year what the total allocations will be.

III. Hospitals, Dispensaries and Other Units

I would again like to stress the possibility of liaison with the General Hospital, Enugu, for the training of nursing staff in the care of leprosy patients.

A. EXISTING MEDICAL FACILITIES FOR NON-LEPROSY CASES. See paragraph I (h).

B. PROPOSED DEVELOPMENT. We are still waiting for the £600 needed for the laundry mentioned in my last annual report.

C. LEPROSY CONTROL. There have been no important changes this year, but this has been primarily because there have been no senior staff available to initiate and supervise needed readjustments of our leprosy control scheme. Because of the way in which leprosy work developed in these Provinces, most clinics are in isolated places and are no longer convenient for the patients. It is desirable to re-site at least some of these clinics at Health Centres and Dispensaries. However, there is often considerable local opposition to this which can only be overcome by patient and repeated explanation of the issues involved. This work is very time consuming and little progress has been made in this direction this year.

D. We are able to offer full medical and surgical care, including reconstructive surgery for our patients. We also co-operate with the Senior Specialist at Uzuakoli in drug research and are doing research ourselves on the causation and treatment of ulcers and design of special footwear and artificial limbs. See appendix I and II.

E. OCCUPATIONAL THERAPY AND VOCATIONAL TRAINING. A vacancy has now been created on our staff for an occupational therapist and we hope that it will be possible to recruit one soon. The major difficulty with respect to this appointment is the provision of quarters. We do not at the moment have any available, and senior staff quarters allocated to the Settlement which have been built at Rural Health Headquarters, continue to be used by other senior staff.

F. AGRICULTURE. The general agricultural training programme is still in the planning stage but I am glad to say that full time agricultural officer has been allocated by the Church Missionary Society for this programme.

IV. Public Health

A. Health of expatriate population.
B. Health of African population. } See C.M.F. 12

V. Vital Statistics

See 1962 report.

VI. Hygiene and Sanitation

A. All clinics are equipped with pit latrines as part of our general effort to teach our patients hygiene.

B. General measures of sanitation in the Settlement and Staff quarters are carried out by the Sanitary Inspectors and gangs of sanitary workers.

C. LABOUR CONDITIONS. Not applicable.

D. SCHOOL HYGIENE. Leprosy Inspectors, visit schools, examine the children and advise treatment when necessary.

E. FOOD IN RELATION TO HEALTH AND DISEASE. Advice is given by the Leprosy Inspectors.

F. HOUSING AND TOWN PLANNING. Not applicable.

G. HEALTH PROPAGANDA AND EDUCATION. The District Leprosy Inspectors and Leprosy Inspectors are engaged in this work.

VII. Port Health Administration and Education

Not applicable.

VIII. Maternity and Child Welfare

Ante-natal and post-natal clinics are conducted weekly for patients as well as staff wives.

XI. Mental Health

Arrangements are now being made for dangerous cases of psychosis to be housed in the Federal Prison here at Oji River and a suitable building is now under construction.

X. Dental Health

At present we have no dental services but a visit from a dentist say, once a month, would be extremely valuable.

XII. Prison

Considerable development has taken place this year in the provision of training facilities for prisoners. We now have workshops where carpentry, basketry and weaving are taught, and a demonstration farm with an agricultural assistant in charge, where improved methods of market gardening and farming are being taught to the prisoners.

XIII. Laboratory Services

There is one Laboratory Technician and one Assistant who do routine smearing, blood, urine, stool and sputum tests. In addition, a large number of smears are done on research cases. (See Statistics).

XIV. Training of Personnel

We continue to help with the training of dispensary attendants and others from the School at Rural Health Headquarters.

XV. Liaison with Private Medical Practitioners

Occasionally, private medical practitioners send us cases for diagnosis and treatment where necessary. We are glad to give whatever help we can.

XVI. Internal Conferences

Nil.

XVII. Distinguished Visitors

(*a*) His Excellency the Governor Sir Francis Ibiam.
(*b*) His Grace the Archbishop of West Africa.
(*c*) The Hon. Minister of Health.
(*d*) The Chairman of Public Service Commission Mr. F. O. Ihenacho.

We have also had large numbers of professional visitors including Mr. C. W. Price, M.D., F.R.C.S., who was formerly orthopaedic surgeon here. His visit was very useful to us and we are grateful to British Leprosy Relief Association for making it possible. Other visitors have come to us from the Northern and Western Regions of Nigeria, Burma, Canada, Cameroon, Republic, Indonesia, India, Iran, Pakistan, Siera Leone, Uganda, U.K. and U.S.A. We have been glad to welcome them all and many have made useful contri-

butions to our work. In particular, I would again like to mention the American orthopaedic surgeons who have at their own expense, come to us to give their skill and experience week by week. I would also like to thank the Senior Medical Officer of General Hospital, Enugu, for his willingness in allowing these surgeons to spend one day per week here.

XVIII. Scientific Publications

Three papers have been published from Oji River this year. One by Dr. Price, a follow-up of the cases which he saw in 1958 and two by the Area Superintendent: Aetiology and Treatment of Plantar Ulcers and Footwear and Prevention of Ulcers. All were published in the *Leprosy Review*.

XIX. X-Ray Services

The X-ray department is now completed and we expect a technologist to be appointed in April, 1963.

XX. Tuberculosis Service

Eight patients suffering from tuberculosis are now on treatment.

ABSTRACTS

Growth (without Multiplication) of Mycobacterium lepraemurium in Cell-free Medium. P. D'ARCY HART and R. C. VALENTINE J. gen. Microbiol (1963), **32,** 43-53

The authors' comment that leprosy bacilli have not been cultivated with certainty in any cell-free medium, and describe their use of a medium which consistently supported considerable elongation of *Mycobacterium lepraemurium*, though without evidence of multiplication. The mean length of the bacilli doubled in about the generation time obtaining in host cells (7 to 14 days), and quadrupled before the bacilli degenerate after about 2 months. The Casal medium they used was composed of:

Difco 'casamino acids'	29 g.
L-asparagine monohydrate	13.5 g.
Anhydrous Na_2HPO_4	2.5 g.
KH_2PO_4	1.0 g.
Trisodium acetate	1.5 g.
$MgSO_4,7H_2O$	0.6 g.
Glycerol	5.3 ml.
De-ionized water up to	1000 ml.
Adjusted with HCl or NaOH to pH	6.2 as required
Autoclaved at 115° for 20 mins.	

The autoclaved solution was distributed in amounts of 4.5 ml., into 28 ml. screw-capped bottles to which were added 0.25 ml. of 5% aqueous solution of albumin (fraction ▽) sterilized by filtration; 1.2 ml. of autoclaved sucrose solution; solutions of any test substances; water to 7.9 ml.; 0.2 ml. of the bacillary suspension from mouse liver homogenate or tissue culture, giving a final total volume of 8.1 ml. containing about 5×10^7, or 10^6—10^7, bacilli per ml. respectively. The final concentration of the ingredients in the complete medium is shown by the authors in a Table, and it is noteworthy that sucrose is 7.4% (w./v.). In 10 figs. in 2 Plates the elongation of bacilli is well shown, and interestingly discussed as to its significance, as well as additional relevant factors.

Morphological and Physiological Aspects of Skin Receptors. K. K. SERGEEV. Vestnikh Dermatologii i Venerologii (Dermatology and Venereology) Moscow 1963, No. 7, pp. 8-13.

The author finds from evidence of his own work and studies of the literature polyvalency and partial specialization of sensitive points and receptors on the skin. He found 4 types of skin receptors, (1) non-specialized polyvalent receptors, (2) partially specialized receptors for mechanical impulses, (3) partially specialized receptors for pain, (4) partially specialized receptors for temperature. Mechanical receptors have a complex spatial placing and move in their own bio-electromagnetic field. Temperature reception depends on differentiated neuroplasm and is modified by a thermo-electric

effect springing from threshold temperature differences in receptor terminals and the irritant. Pain is received by silver-staining basal neuroplasm responding to traumatic irritation. Reception of mechanical impulses is the most important in the process of learning and in work. There are no special cells nor capsules which can determine specificity of function in skin receptors as a whole.

REVIEWS

The Pathogenesis of Leprosy. Ciba Foundation Study Group No. 15, published by Messrs. J. & A. Churchill, 104 Gloucester Place, London, W.1. Price 15s. net.

This is a small booklet of 101 pages, measuring 12.5 by 19 cm. and therefore very handy and suitable for carriage in the pocket. It contains a very valuable report of the Ciba Foundation study group under the chairmanship of the late Dr. J. A. DOULL, whose very useful closing remarks are given. The main part of the booklet is devoted to papers and discussion on the following:

(1) Experimental Observations Related to the Histopathology of Leprosy, by G. WEDDELL, E. PALMER, R. J. W. REES, D. G. JAMISON.

(2) Cytopathology of the Virchow Cell of human leprosy, by E. M. BRIEGER, J. A. ALLEN.

(3) Applicability of Experimental Murine Leprosy to the study of human leprosy, by R. J. W. REES, M. F. R. WATERS.

(4) Experimental studies on human leprosy, by K. J. RANADIVE.

(5) Leprosy bacilli on mouse footpads, by C. C. SHEPHARD.

All these subjects are of first importance at the present time of onward march to the understanding of the pathogenesis of leprosy, and all will be most grateful to the Ciba Foundation for arranging and carrying through this symposium. This is undoubtedly a booklet which everyone interested should possess and study.

Alone No Longer, by STANLEY STEIN with LAWRENCE G. BLOCHMAN 1963, Funk & Wagnalls Company, Inc. New York, $5.00, p. 384, 22 illustrations, 4 pp. of Index.

The subtitle of this book is 'The story of a man who refused to be one of the living dead' and refers to Stanley Stein who writes of the disease leprosy, or 'Hansen's disease' as he prefers to call it, from the inside, as a sufferer from the disease who has lost his sight from it, has shared the experiences of other patients, and above all by editing the magazine *The Star* from Carville hospital has conducted a lifelong battle to obtain a humane and enlightened attitude to those who suffer from it. It becomes abundantly clear as he develops his story that there is ample need for such a battle. The battle is not won yet, but Mr. Valiant-for-Truth, who is Stanley Stein, has earned the gratitude of every leprosy patient who is afflicted by the crass fear and inhumanity with which every sufferer is liable to be treated, even yet.

The dedication of this book is 'To my mother of blessed memory whose quiet courage and Maccabean spirit are ever my inspiration'. This absorbing and inspiring book by Stanley Stein will show the

reader that his mother's spirit has descended to Stanley Stein, and, who knows, may well spread to the reader.

There are 24 Chapters in the book. The First Chapter tells the story of his first arrival at the hospital at Carville, La. on March 1st, 1931, where his natty suit at first caused him to be mistaken by his fellow patients as a New York dude millionaire! He settled down at the leprosarium and has seen it grow from the somewhat primitive institution it was then to the magnificent hospital it has become. He has passed through the epoch-making days of the discovery of the curative action of the sulphones at Carville, but alas he seems to have come too late to get cure from the sulphones and in fact lost his sight. He has continued as Editor of the *Star* all these years and used it to spread the light of knowledge about the disease.

This absorbing book by Stanley Stein only needs to be begun. The reader will finish it with eagerness, and praise God.

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