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EDITORIALS

Drug Resistance in Leprosy

One of the chief bugbears in modern medicine, especially in diseases which require prolonged treatment, is the development of strains of the infecting organism which are resistant to the drug used. What evidence is there that drug resistance may develop in leprosy? As *Myco. leprae* has not so far been effectively cultivated outside the human body, there is no bacteriological indication as to whether there is more than one strain, or as to whether a universal strain varies under certain circumstances. Nor is there any clinical or epidemiological evidence that the gravity of the disease, and the variety in its types and forms, correspond with different strains. These diversities appear rather to be contingent on degrees of resistance—on the soil rather than on the seed. One child of an infective mother will develop the lepromatous type and another a mild tuberculoid, although both have been subjected to intense infection from the same source. The fact that the majority of advanced lepromatous cases under treatment with sulphones continue to improve steadily over long periods, sometimes of ten years or more, would have led to the hope that *Myco. leprae* was incapable of forming resistant strains; but there seems to be general agreement that under treatment with thiosemicarbazone initial improvement comes to an end after a few months, and the patient tends to relapse. Is this the result of drug-resistant strains, or is there something else that blocks the early effectiveness? In our present ignorance of the mode of action it is impossible to say with any certainty.

An important question arises as to whether the sulphones produce drug resistance, and if so under what circumstances. Most of those with any extensive experience of sulphone treatment of leprosy have had patients who improved up to a point and then appeared to make very little or no further progress. In the writer's experience this has generally been connected with two things: irregularity of treatment and absence of physical exercise. Wolcott and Ross[1] found a number of instances of rapid extension of the leprous process in patients receiving continuous sulphone and other treatment, in whom the disease had reached a stage of apparent quiescence. The only possible cause found was that a few of these had experienced some increase of emotional strain. Elsewhere Doull and Walcott [2] reported relapse in 6 of 33 patients who were followed up for one to five years after apparent arrest.

This is in marked contrast to the findings of Lowe[3] in Nigeria. Out of 139 lepromatous patients discharged there was slight

bacteriological relapse in 13. Of these, four became rapidly negative under treatment five became negative without treatment, but in none was there a serious relapse. Garrett[4], after discharging for 3½ years an average of 3,000 patients a year, found an average relapse rate of 7 per cent. These were in three types of patients: (a) In those previously treated with hydnocarpus oil and apparently inactive, many had had a course of dapsone of only one year or less; (b) in clinically tuberculoid cases, not completely typical, either with not very clearly defined edges or with lack of healing centre, in whom response to treatment is usually dramatic. Lesions disappear in a few months, but lacking an initial positive smear, they were given a relatively short course of dapsone, usually 18 months; (c) those not attending regularly for treatment due to laziness or personal difficulties. See also the Owerri Report, page 119 of this issue.

The Editor would welcome evidence and experiences from other workers under the following headings: (1) patients who have become bacteriologically negative (routine examination) under sulphones and have then relapsed; (2) whether such patients have yielded to further treatment with sulphones; (3) patients who improved at first up to a point with sulphones and then failed to make further progress over years of further sulphone treatment; (4) whether these patients undoubtedly *had absorbed* regular treatment; (5) other particulars.

* * * *

VII International Congress

At the Madrid Congress in October, 1953, an invitation was received from the Indian Government, and accepted, to hold the seventh international congress on leprosy in India. The first international congress was held in Berlin in 1897, where there was a pronouncement in favour of rigorous isolation of leprosy patients, which was followed by a marked diminution of leprosy in Germany and Central Europe. The second congress was in Bergen in 1909, where the same pronouncement was ratified. This was followed by complete control and near disappearance of leprosy in Norway. The third congress was in Strassburg in 1923, where the tuberculoid form of leprosy was described, leading to a modification of measures for prophylaxis. In 1931 a number of leprologists were invited to a conference in Manila under the auspices of the Leonard

(1) Internat. Jl. of Lep. (1953), Vol. 22, p. 437.
(2) New England Jl. of Med. (1956), Vol. 254, p. 20.
(3) Internat. Jl. of Lep. (1955), Vol. 23, p. 183.
(4) Lep. Rev. (1956), Vol. 27, p. 59.

Wood Memorial, which led among other things to a new classification of leprosy, and to the foundation of the International Leprosy Association. One of its functions was to arrange for quinquennial international congresses in different countries, the governments of which would act as hosts and invite other countries to send delegates. The first of these, that is the **fourth** international congress, was held in Cairo in 1938. There, it was arranged that the next congress should be held at Paris in 1943, but this was rendered impossible by the war, and the fifth Congress met in Havana in 1948 at the invitation of the Government of Cuba. There invitations for the next congress were received from India and from Spain, but by a majority vote it was decided that the sixth congress should be held in Madrid in 1953. There the invitation from India was received for the 1958 congress, and a new invitation was received from Japan. The former of these was accepted, the hope being expressed that a subsequent congress would meet in Japan.

It is understood that the location of the seventh congress will probably be **New Delhi** and that it will probably meet in **November, 1958.**

There was considerable criticism of the last two congresses, and steps are being taken to modify accordingly the arrangements for the Delhi meeting. The chief modifications suggested are as follows:—(1) the scientific preparations to be in the hands of the International Leprosy Association from the first; (2) preparatory panels on as many as possible of the subjects chosen to be formed beforehand, with the object of collecting, discussing and co-ordinating information and opinions prior to the congress; (3) selected workers to be asked to prepare and read papers on each of the selected subjects at the main sessions of the congress, these papers thereafter to be open to general discussion; (4) the results of these papers and discussions would then be co-ordinated with draft resolutions by selected commissions, the nucleus of each commission being the corresponding preparatory panel. Provision would be made for reading of other papers provided they conformed to the regulations regarding length, and were received before the dated decided. We hope to publish further information as soon as it is available.

* * * *

Testing New Drugs for Leprosy

A sub-committee of the Colonial Medical Research Council has been formed to initiate and co-ordinate research in leprosy in the U.K. and the colonies. One of its activities is to form panels (a)

to advise on drugs considered suitable for "pilot" testing as to their value in the treatment of leprosy; (b) to arrange for further controlled tests of drugs, the pilot tests of which had given evidence of hopeful results; and (c) to assess statistically and otherwise the results obtained in these controlled experiments.

The compound of diphenylthiourea reported on in this number is a good example o
testing but in a limited controlled experiment, that it is well worthy of wider trials. Arrangements for these trials are already under way. The three chief weaknesses of sulphone treatment are occasional toxicity, erythema nodosum or more severe lepra reaction, and the slowness of elimination of bacteria. If the findings with this new compound on these three scores are widely confirmed, and if its usefulness is not limited by the development of drug resistance, then another considerable advance may be recorded in the treatment and control of leprosy.

CLINICAL TRIAL OF DIPHENYL THIOUREA COMPOUND SU 1906 (CIBA 15095E) IN THE TREATMENT OF LEPROSY

PROGRESS DURING THE FIRST YEAR

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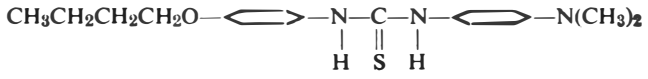
Introduction

The fact that certain compounds of thiourea exhibit antituberculous activity, but *in vitro* and *in vivo*, was noted by Mayer, Eisman and Kokopka (1953). The clinical trial of three of these compounds in the short term treatment of tuberculosis was reported by Schwarz, Owen and Gierson (1954), who found one of them, a derivative of diphenyl thiourea, particularly promising. After the administration of this substance for periods up to four months in a group of 20 patients suffering from tuberculosis, of whom 19 were in an advanced stage of the disease, and 11 were resistant to other forms of therapy, improvement as shown by X-rays was evident in 16 patients, sputum had become negative for M. tuberculosis in 10 patients, and cultures were negative in 6 patients. There was no appreciable evidence of toxicity at the dosages employed. As a result of these findings a pilot trial of the drug in

leprosy treatment was undertaken, and has been in progress for 16 months. Findings recorded here are in the nature of a progress report, the period of trial sufficing to make some assessment of toxicity and of short term activity against *M. leprae.*

Chemistry

The substance concerned is 4,butoxy-4',dimethylaminodiphenyl thiourea (or thiocarbanilide), and has the following structural formula.



It is a white, almost tasteless, powder, melting at 91-94 degrees C., sparingly soluble in water, but very soluble in acetone. There is as yet no ready means of estimating its concentration in body fluids. It is prepared in the form of tablets containing 250 milligrammes.

Choice of Patients

The drug was administered in the first place to a small group of able-bodied adult leprosy patients who had had no previous chemotherapy. The group was made up of lepromatous cases, either early or of moderate severity, and an approximately equal number of patients with active spreading tuberculoid lesions, the latter being included to give speedy evidence if the drug proved inactive. As evidence began to appear that the drug was not unduly toxic and also possessed activity, patients with lepromatous leprosy of greater severity were added, and the group further expanded by the addition of children and a few borderline and indeterminate cases. A biopsy was taken in all cases to remove any doubts as to classification and also to provide a check on progress. In addition, each patient was matched against a control patient who was taking routine DDS treatment, and was comparable in age, sex, type and extent of leprosy and also in reaction to lepromin.

Dosage

In treating patients with tuberculosis, Schwarz and his colleagues commenced with a dose of 3 gm. of SU 1906 daily, given orally in three divided doses, and then increased this by 1.5 gm. at weekly intervals up to a maintenance dose of 6—9 gm.

daily. During the short period of trial reported, no significant toxic effects were encountered on this dosage.

In leprosy patients, with limited supplies, and a possible long term experiment in prospect, it was thought desirable to commence treatment at a lower level, and increase it more slowly. A daily dose of 1 gm., given undivided, was selected empirically, and this was increased by 0.5 gm. daily at fortnightly intervals, a close watch being kept on tuberculoid cases for signs of resolution as a group. Such signs did in fact begin to appear on a daily dose of 1.5 gm., and double this dose, i.e. 3.0 gm. daily was chosen as the standard maximum maintenance dose. Dosage has been maintained between these two levels in the case of adults, and children have received 0.5, 1.0 or 1.5 gm. daily according to age. In all cases there has been a rest from treatment on one day a week.

Toxicity

As information regarding SU 1906 was meagre, caution was exercised in the early stages of treatment, and careful laboratory control was maintained, with special attention to the blood, and to liver and kidney function. This drug has now been given to over 40 patients for periods of from 4 to 16 months, and has been well tolerated. There have been no signs of gastric or intestinal irritation, and up to the present there has been no evidence of any kidney damage, hepatic insufficiency, or blood dyscrasia for which the drug could be held responsible. These findings agree with those of Schwarz. In addition there has hitherto been no case of drug fever or dermatitis. In view of the relationship between this substance and thiouracil, a watch has been kept for any sign of thyroid insufficiency, but none has been found. All patients, apart from intercurrent infections, have remained in good health, and it has not been necessary to withdraw anyone from treatment with this drug. Occasional complaints have been made of a mild but irritating papular skin eruption, but this has always been of short duration, and it has proved impossible to relate it definitely to the taking of SU 1906, in that it disappeared within a few days regardless of whether the drug was given or withheld, and also it was seen among control patients. This, together with mild degrees of anaemia and urticarial eruptions, which have also been seen from time to time, must be regarded as inevitable in an area where malaria, filariasis, and virus infections are rife. These incidentals have not modified the opinion that this drug is markedly free from toxic action at the dosage levels employed, and in that respect

it compares favourably with the sulphones and with thiosemicarbazone.

Progress of Leprosy

In assessing the progress of leprosy during treatment with SU 1906, 31 patients were available for study, none of whom had had previous chemotherapy. Of these, 21 had received SU 1906 for more than 12 months, 27 for more than 6 months, and all for more than 4 months. They are classified as follows:

Lepromatous	17
Tuberculoid	8
Indeterminate	3
Borderline	3

(a) *Lepromatous cases*

The 17 cases formed a mixed group, sub-classified as follows:

Advanced diffuse or nodular leproma ...	3
Moderately advanced ditto	7
Early diffuse leproma	2
Lepromatous macules	5

The average age of this group was 29 years, the average duration of the disease, as given by the patients, was 15 months. Although some infections were very recent, the group also included two which were of quite exceptional severity.

Without exception, every patient has shown clinical improvement, with reduction in infiltration, flattening of nodules, and loss of erythema and fading of macules. In twelve cases (over 60 per cent), clinical improvement could be detected within three months of starting treatment, and was evident in all cases within six months. In two cases with ulcerating nodules, healing of the lepromatous ulcers occurred rapidly.

Details of changes in the number of bacilli in routine smears are given later. Here it suffices to say that a reduction in numbers of bacilli in smears has taken place in every patient, and has followed the pattern familiar in the chemotherapy of leprosy. In patients with a bacterial index of less than the maximum, bacteriological improvement kept pace with clinical improvement. Patients with maximal bacterial index demonstrated the usual time lag before a decline in numbers of bacilli became evident in routine smears, but changes in the morphology of bacilli became evident early in these cases as it did in others.

Progress in these patients was particularly marked during the first nine months. After that time, although with the exception of one case, clinical progress has continued uninterrupted, there has been a perceptible falling off in bacteriolgical improvement in a few cases. The matter is considered in greater detail later.

(b) *Tuberculoid cases*

All eight patients have markedly improved. In seven, skin lesions have become flat and inactive (1 after 4 months, 1 after 6 months, 2 after 10 months and 3 after 12 months). Signs of resolution in macules appeared early, in two cases within one month of starting treatment, and were apparent in all cases within four months. The process of resolution did not in some cases appear to be identical with that seen during sulphone treatment, loss of erythema being a prominent early sign, associated with or followed by a fine desquamation and gradual flattening and loss of thickening in macules. Signs of neuritis took longer to resolve, but in all cases had disappeared by the end of one year, in five cases after a period of exacerbation.

(c) *Borderline and Indeterminate cases*

All have shown improvement. The three indeterminate cases displayed early loss of erythema and fading of macules, which are now considered residual in all cases (1 after 6 months, 2 after 10 months). Borderline cases have shown dramatic improvement, with marked decline in bacilli and resolution of skin lesions, in two cases following an acute exacerbation.

All the 31 patients have thus shown improvement. Biopsies repeated after 6 months in 12 cases yielded convincing evidence of resolution in every case. Photomicrographs from two of these are illustrated in Figures 1 to 4.

The series has included eight children. All have tolerated the drug excellently and without exception have shown gratifying improvement. Three of them were lepromatous cases, already of some severity.

Complications during treatment

Erythema Nodosum Leprosum

Only one lepromatous case suffered from typical erythema nodosum. It appeared at the third month on a dose of 3.0 gm. daily, and was of moderate severity and short duration. There-

after progress was accelerated for a time in spite of reduction of dose to 1.0 gm. daily. Three months later, following a severe attack of influenza, the same patient showed some exacerbation of his condition, but this was again of a temporary nature only, and on increasing dosage again, ground lost was made up.

Increased activity in lesions

Two patients, classified as macular leproma both clinically and histologically, after showing clinical improvement and a reduction of bacilli in routine smears, underwent a phase of heightened activity in the third month, with the eruption of fresh lesions of borderline type, and confirmed as such histologically. Thereafter resolution was rapid. Cases borderline at the outset proceeded to resolve without any preliminary phase of increased activity, but one of them, at the seventh month, when routine smears had become negative, had an eruption of flat well defined macules, which then proceeded to resolve rapidly. In two of these patients the shift in clinical appearances towards the tuberculoid form was accompanied by lepromin conversion from negative to a mild positive. These changes are of interest though of no direct importance from the standpoint of this trial. Apart from these cases, resolution of skin lesions has been uninterrupted in all patients.

Neuritis

Twelve of the 31 patients have complained of neuritis at some time or other during treatment. It was seen as early as the 3rd month, but was most prominent between the 7th and 10th months. In one case this was a sudden acute neuritis developing in a patient with previously unthickened nerves (a borderline case at the third month). In nine patients it represented an exaggeration of thickening and tenderness in nerves already involved before treatment started. In the remaining two cases it was associated with no detectable pathological changes. This complication is common in all forms of chemotherapy in leprosy. What was notable about it in patients on SU 1906 was its frequency during the first year of treatment, and the fact that at the end of one year it had ceased. This may be a chance finding, but if later it proves to be more generally applicable, it is a fact of importance. In our cases neuritis was either mild or of moderate severity, and though in two patients it led to some degree of foot drop, this was only temporary.

Neuritis was relieved following a reduction of dosage in five patients, and in the remainder it disappeared on its own. After one year's treatment no patient complained of it.

Rate of Progress: Comparison with controls

The progress of patients receiving SU 1906 can be compared with that of matched control patients receiving DDS as follows.

(a) *Lepromatous cases*

(i) *Clinical improvement*

Considering firstly the 12 patients who have had treatment for more than 12 months, results are as follows:

	SU 1906	DDS
Much improved	7	6
Improved	5	6
Slightly improved	0	0
Stationary	0	0

The remaining five patients in the series, with periods of treatment ranging from 4 to 9 months all show good progress, with little difference between trial patients and their controls.

(ii) *Bacteriological improvement*

This is by far the most important aspect of this trial, and it is worth while giving details of changes which have occurred patient by patient. These are presented in Tables I and II, the former giving the results in patients on SU 1906, the latter giving corresponding figures for control patients placed in the same order. The tables give a bacteriological index for each patient, taken at the onset and at three-monthly intervals during the period of trial. The figure given for Bacterial Index is simply the calculated average of the findings of multiple smears, in which the maximum degree of positivity has been recorded as 4, indicating a slide with innumerable bacilli in every field, 0 represents a negative finding, 1 a slide in which bacilli are scarce, and 2 and 3 are intermediate between the extremes. The figure given at each quarterly interval is the average of *all* smears undertaken on the patient during the three months ending at that date. This method of calculation offers a fair and simple means both of registering progress and of comparing one individual with another. It can also be applied to complete groups of patients.

TABLE I

BACTERIAL INDEX, SU 1906 TREATMENT

SU 1906 No.	Months of Treatment						Decrease
	0	3	6	9	12	15	
1	3.3	2.8	2.0	1.9	1.7	1.4	1.9
2	3.2	2.2	2.1	1.6	1.3	1.4	1.8
3	2.3	1.8	1.4	0.9	0.8	1.1	1.2
4	0.8	0.2	0.1	0	0	0	0.8
5	4.0	3.8	3.2	2.8	3.0	2.9	1.1
6	2.8	1.8	1.4	0.6	0.4		2.4
7	3.8	2.8	2.5	2.4	3.1		0.7
8	3.8	2.8	2.3	1.4	1.8		2.0
9	3.5	2.2	1.6	2.0	1.5		2.0
10	4.0	4.0	2.8	3.5	2.3		1.7
11	4.0	2.8	3.1	2.3	2.5		1.5
12	2.3	1.0	0.2	0.2	0.2		2.1
13	2.0	2.0	1.8	0.6			1.4
14	3.5	2.8	2.0				1.5
15	2.0	1.8					0.2
16	3.5	3.0					0.5
17	2.0	1.2					0.8
						Group decrease	23.6
Group average	3.0	2.6	1.9	1.6	1.6	1.4	

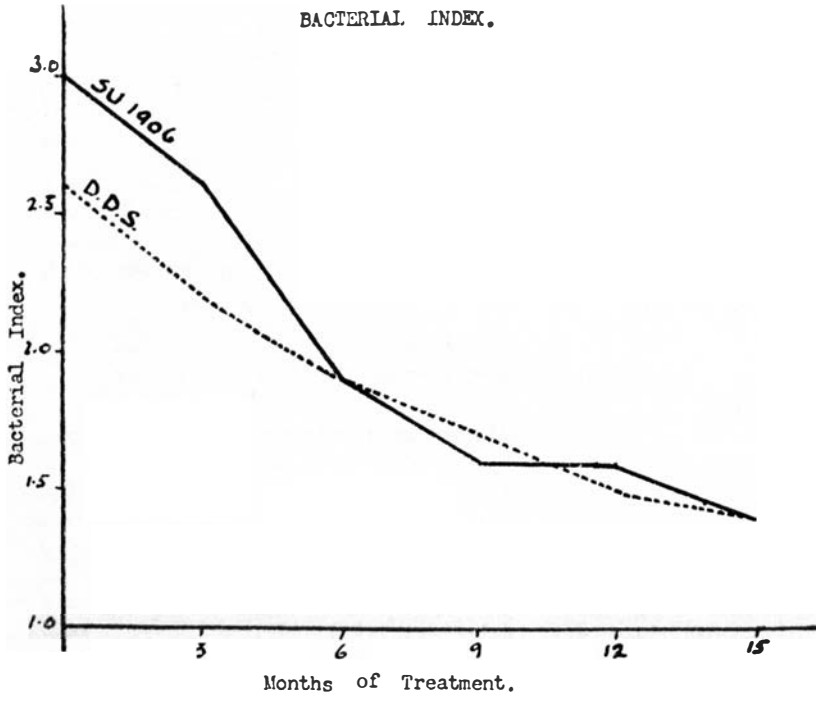
TABLE II

BACTERIAL INDEX, CONTROLS ON DDS TREATMENT

Control No.	Months of Treatment						Decrease
	0	3	6	9	12	15	
1	3.0	2.8	2.3	2.1	2.0	2.7	0.3
2	2.5	2.5	1.5	2.0	1.5	1.3	1.2
3	2.0	2.3	1.7	1.1	0.8	1.1	0.9
4	0.6	0.3	0	0	0	0	0.6
5	3.0	3.3	2.3	2.0	1.3	1.8	1.2
6	2.3	2.3	2.3	2.3	2.3		0.0
7	3.0		2.3	3.0	3.0		0.0
8	2.8	2.3	1.5	1.5	1.4		1.4
9	2.5	2.8	2.3	1.8	1.1		1.4
10	4.0	2.0	2.8	1.4	1.4		2.6
11	4.0	2.3	2.3	2.0	1.5		2.5
12	2.3	2.3	2.7	0.9	1.7		0.6
13	2.3	2.5	1.8	1.8			0.5
14	2.8	1.8	1.4				1.4
15	1.5	0.9					0.6
16	3.3	2.8					0.5
17	1.8	1.3					0.5
					Group decrease		16.2
Group average	2.6	2.2	1.9	1.7	1.5	1.4	

A comparison of Tables I and II is of interest. It will be noted from the first column that at the outset the trial patients were as a group more heavily infected than the controls, who thus had a slight bias in their favour. At the end of the period covered by this progress report, both groups had shown considerable progress, but trial patients showed a corporate fall in Bacterial Index which exceeded that exhibited by controls by nearly 50 per cent.

In neither group was progress maintained at a steady level. This is clear from Figure 5, in which the quarterly indices of each are consolidated as a single average figure, so that it is possible to compare the progress of the two groups quarter by quarter.



This graph illustrates the very good progress displayed by trial patients during the first nine months, progress decidedly greater than that shown by control patients taking DDS treatment during the same period. It also illustrates a falling off in progress in both groups, especially noticeable after the ninth month, and thrown into greater relief among trial patients by their earlier progress. Of the 12 lepromatous trial patients who have completed 12 months or more of treatment, 7 have continued to show uninterrupted progress, while 5 have shown a falling off. Heavy infections are found in both these groups. but it is noticeable that the latter group contains the patients with the longer histories of infection. Recent infections, regardless of their severity, have continued to do well.

(b) *Tuberculoid Cases*

Improvement among the two groups was very similar.

	SU 1906	DDS
Becoming residual:		
at 4 months	1	0
at 6 months	1	1
at 10 months	2	3
at 12 months	3	2
Still active:		
after 6 months	1	2 (At 10, 12 months)

(c) *Borderline Cases*

Improvement was almost identical between the two groups.

	SU 1906	DDS
Skin lesions residual, bacteriologically negative	1	1
Much improved	1	1
Improved	1	1

N.B.—As noted above, one trial patient underwent an eruption of flat macules during the seventh month. Her control patient did exactly the same!

(d) *Indeterminate Cases*

Progress was almost identical between the two groups.

	SU 1906	DDS
Residual	3 (At months 7, 10, 10)	3 (At months 6, 9, 9)

Reviewing the two groups as a whole, it may be stated that where tuberculoid, borderline, and indeterminate cases were concerned, progress during SU 1906 therapy was closely comparable with that exhibited by controls receiving DDS treatment. Where lepromatous cases were concerned, the clinical progress of patients receiving SU 1906 was as good as that exhibited by controls, and during the first nine months bacteriological improvement was in fact better; and though some slackening in progress became evident in some patients later, progress after 15 months was still as great as that seen in controls.

SU 1906 in patients already treated with DDS

As a supplementary to these findings it may be of interest to record the progress of a separate group of 10 patients who were given SU 1906 therapy after varying periods of treatment with DDS. These belonged to the small minority of leprosy patients whose progress under DDS is not entirely satisfactory. They were given SU 1906 experimentally either because resolution was unduly delayed, or on account of frequent erythema nodosum, or nerve involvement which was advancing in spite of treatment.

1. A group of 5 severe lepromatous cases who were making little if any progress after 45 to 57 months of DDS treatment, all of them still showing normal looking bacilli in routine smears, were given SU 1906 in doses not exceeding 1.5 gm. daily for periods of 9 to 15 months. In two cases DDS was given concurrently. Although erythema nodosum occurred from time to time in these patients, this dose was tolerated, and all five cases have shown continued improvement both clinically and bacteriologically. In three of them progress has been accelerated during this period.

2. Two indeterminate cases exhibiting fresh macular activity after 40 and 50 months respectively of DDS treatment, have shown marked improvement after 6 months treatment with SU 1906.

3. Three patients suffering from persistent neuritis, two of them during DDS treatment, with advancing involvement of both ulnar nerves in spite of treatment, were given SU 1906 therapy in doses not exceeding 1.5 gm. daily. Over periods of 5 to 8 months all have shown improvement in the leprosy condition generally, and also in the neuritis, with cessation of subjective symptoms, decline in swelling and tenderness, and arrest of the advancing muscle involvement.

These results are given for what they are worth. The good results may be a coincidence, but they do at least indicate that previous DDS treatment does not inhibit the therapeutic activity of SU 1906, and that small doses may have virtue.

Discussion

Caution is needed in assessing these findings. This is a progress report in a pilot trial, and neither numbers of patients involved nor the period of observation are adequate to permit anything more than a first impression. It should also be noted that leprosy in E. Nigeria is notoriously amenable to treatment, and it does not follow that such satisfactory results are to be expected everywhere. Nevertheless, patients were chosen with care, and are a fair selection of the clinical varieties of leprosy as found anywhere. Also, any local advantages possessed by the trial patients were also shared by their controls. In view of these considerations it may be stated with confidence that this drug introduces a class of therapeutic agents urgently needing further study by those interested in the treatment of leprosy.

SU 1906 is not the only member of this family to possess activity against mycobacteria. *Buu-Hoi, Nguyen-Ba-Khuyen, and Nguyen-Dat-Xuong (1955) report good results in 13 leprosy patients treated for six months with the 4,4′-diethoxy compound of diphenyl thiourea. Schwarz and his colleagues also used a more complicated derivative of this substance in four tuberculosis patients with good effects. All three compounds appear to possess the property of low toxicity. It is evident that this class of compounds is potentially of great promise, and if a member of it can

* See pages 126-7.

be discovered which can be produced cheaply, and which on a long term basis maintains the promise shown so far by SU 1906, a real advance will have been made.

It has been suggested that the biological activity of SU 1906 is similar to that of thiosemicarbazone. Differences in molecular structure between the two substances are considerable, and evidently sufficient to provide a wide difference in toxicity, but if there is any basis of truth in this suggestion, the possibility that drug resistance will develop to SU 1906 cannot be ignored.

The falling off in rate of progress in some lepromatous cases after the 9th month of SU 1906 treatment needs to be considered against this background. In so small a group it may have no permanent significance. In our experience, relatively few heavily infected lepromatous cases proceed by a process of steady improvement to complete resolution. Those that do are generally infections of short duration. Progress more commonly has its ups and downs, and the reasons for this have not yet been fully studied. Several workers have described seasonal variations in the progress of leprosy. They are seen also in Nigeria, and it is noteworthy that with the onset of the rainy season our trial patients have entered the least favourable period of the year. Also, the influence on leprosy of intercurrent virus infections has not yet been assessed. Such infections are common in West Africa and may have some bearing on seasonal variations in progress. One trial patient reacted badly to an attack of influenza during a small epidemic in which several others were involved. Furthermore, there is surely significance in the fact that the longer a leprosy infection has been established, the less likelihood there is that improvement under chemotherapy will be steady and uninterrupted. Nevertheless, the possibility cannot be excluded that we are witnessing the beginnings of drug resistance in a few of our patients. For them the next six months will be the crucial period of this trial.

It is worthy of note that SU 1906 can have virtue in patients in whom the response to DDS has left something to be desired, and can help both in the direction of hastening resolution and in relieving persistent neuritis. The further study of this drug in conjunction with DDS is needed. Its lack of toxicity and its early activity would appear to make it suitable for initiating treatment, and its use in alternation with DDS may possibly be preferable to its use in combination with it. This is one of the matters worth considering in the wider trials which are now called for, along with

the study of the optimum range of dosage and the use of SU 1906 in combination with drugs other than DDS.

Summary

A progress report is presented of a clinical trial in leprosy treatment of SU 1906, a derivative of diphenyl thiourea.

This substance was administered in doses of 1.5 to 3.0 gms daily to 31 leprosy patients, none of whom had had any previous chemotherapy. Patients were matched individually against controls receiving routine DDS treatment, and a progress report written when the trial had been in progress for 16 months, and 21 of these patients had received SU 1906 for one year or longer. A brief supplement reports on the progress of an additional 10 patients who were given SU 1906 during the same period of trial, but who had previously received DDS treatment for varying lengths of time.

The drug was found to have negligible toxicity at the dosages used, and to possess activity against *M. Leprae* during the first year of treatment very similar to that displayed by DDS. In lepromatous cases progress during the first nine months was greater than among controls, but in some patients it was not subsequently maintained at this level. The possible implications of this are discussed, and the use of the drug in combination with DDS and other chemotherapeutic agents advocated in wider trials.

ACKNOWLEDGEMENTS

This trial was undertaken at the suggestion of the late Dr. J. Lowe when Medical Secretary of the British Empire Leprosy Relief Association. Both at its inception and during its progress valuable advice and encouragement have been given by Dr. F. Hawking of the Medical Research Council, and grateful thanks are due to him. We also acknowledge with gratitude the gift by CIBA Laboratories Ltd. of the SU 1906 used in this experiment.

Thanks are also due to the World Health Organisation, whose grant of a Fellowship enabled one of us (G.C.) to share in this work.

It is also a pleasure to acknowledge the help given by many friends and colleagues, and especially Dr. D. Cannon, Chief Pathologist Federal Government, and Dr. G. T. Barnes, Senior Pathologist Western Region, Nigeria, for expressing an opinion on progress as shown in histological sections; Dr. A. Kissaun and Dr. G. Moneta for the critical assessment of controls in relation to corresponding trial patients; Dr. G. T. Barnes and Mr. S. Drewett for photomicrographs; Mr. S. Drewett, laboratory Superintendent and his staff, especially Mr. G. O. Okezie, for a great deal of laboratory work and personal interest in the patients; and also Mr. L. Anyanwu and the patients themselves for their constant cheerful co-operation.

Thanks are also due to the Secretary for Health, Federation of Rhodesia and Nyasaland, for permitting Dr. Currie to associate his name with this paper; and to Dr. K. Seal, Leprosy Adviser, and to Dr. McLetchie, Director of Medical Services, Ministry of Health, E. Region, Nigeria, for permission to publish.

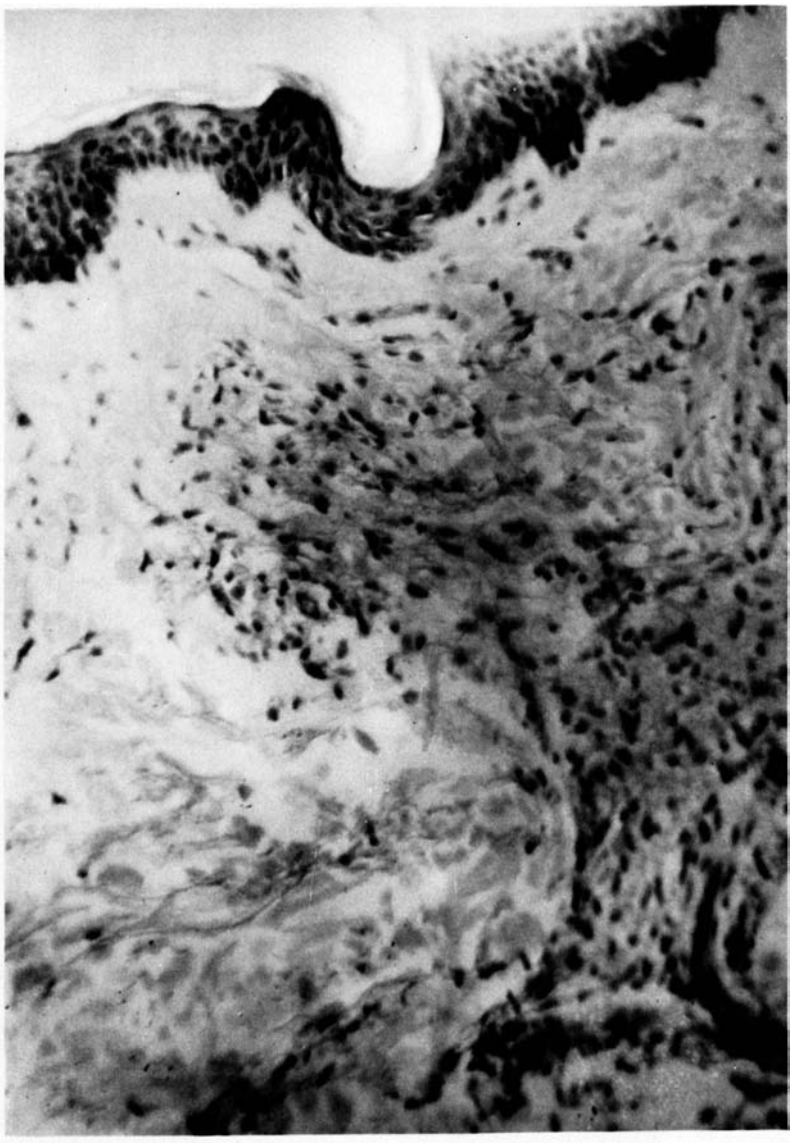


Fig. 1

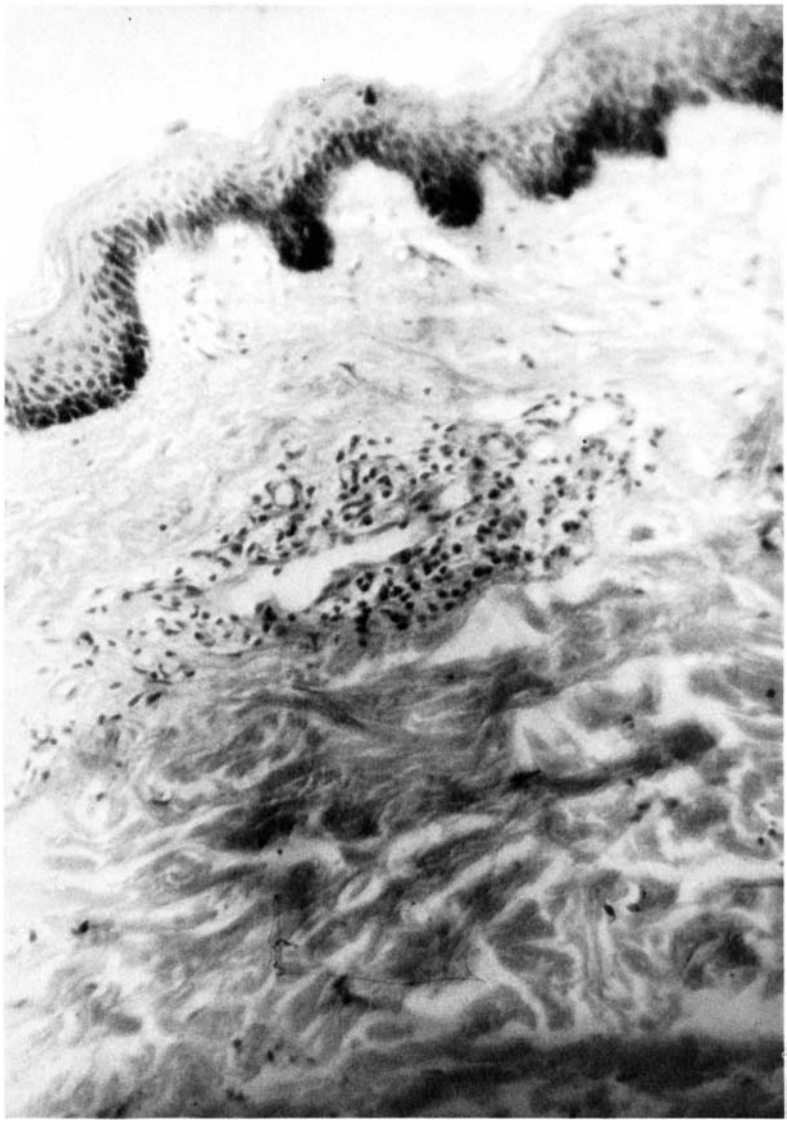


FIG. 2

Fig. 3

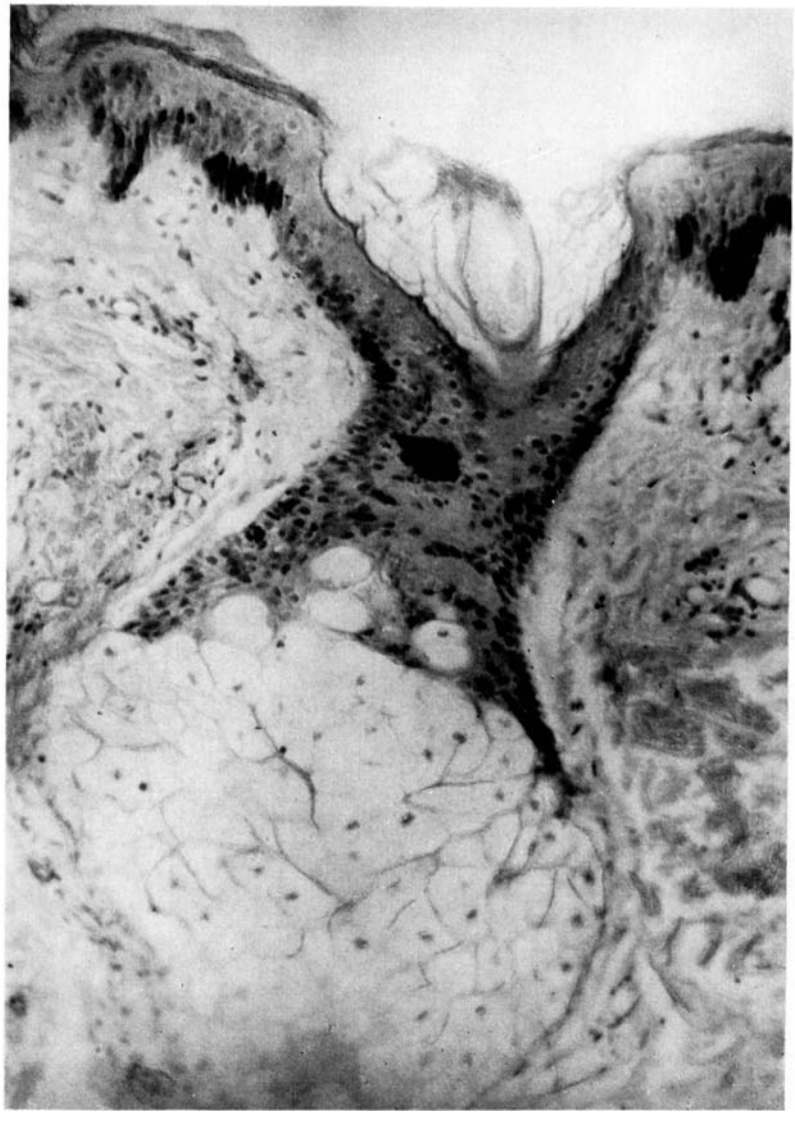


FIG. 4

REFERENCES

(1) BUU-HOI, NGUYEN-BA-KHYEN, and NGUYEN-DAT-XUONG (1955). Bulletin de L'Academie National de Medecine, **139**, 275.
(2) KONOPKA, E. A., GIST, T., EISMAN, P. C., and MAYER, R. L. (1955). Proc. Soc. Exp. Biol. & Med., **89**, 388.
(3) MAYER, R. L., EISMAN, P.C., and KOKPKA, E. A. (1953). Proc. Soc. Exp. Biol. & Med., **82**, 769.
(4) SCHWARZ, J. A., OWENS, G. J., and GIERSON, H. W. (1954l. Tr. of the 13th Conference on the Chemotherapy of Tuberculosis, Feb. 8th, 1954, Veterans' Association, U.S.A.

Fig. 1. Diffuse lepromatous leprosy of moderate severity in a male aged 18 years. 6 months history. Smears 4+. Biopsy taken from the back before starting SU 1906 treatment, and illustrated here, shows extensive infiltration in the upper layers of the corium. The characteristic foamy appearance of the granuloma and the sub-epidermal clear zone are well illustrated.

Fig. 2. Six months later, biopsy at a site immediately adjacent to the former one shows marked shrinking of the granuloma, leaving scattered small foci such as that illustrated here. Foci are localised around blood vessels, which are dilated, and their cellular elements are frequently more sparse than in the illustration. Smears still 3+, but bacilli show degenerative changes in marked degree.

Fig. 3. Advanced lepromatous leprosy in a male aged 25 years, with enormous numbers of bacilli at every site tested in spite of a history of only 8 months. Biopsy from the right thigh taken before starting SU 1906 treatment shows typical lepromatous infiltration involving the entire thickness of the corium.

Fig. 4. Biopsy taken seven months later from a site immediately adjacent to the former one shows very marked resolution, the infiltration persisting only as multiple small foci, vascular, and with relatively few cellular elements. They may be seen on either side of the hair follicle illustrated here, their paucity in this situation indicates the degree of resolution which has occurred. Smears still read as 4+ and show some normal looking bacilli but much acid fast debris.

REVIEWS

International Journal of Leprosy, Vol. 23, No. 3, July-Sept., 1955.

The orginal articles are as follows:—

J. M. M. Fernandez writes on *Influence of the Tuberculosis Factor on the Clinical and Immunological Evolution of Child Contacts with Leprosy Patients.*

The evolution is described of 83 children who had lived in contact with open, lepromatous patients, and whose exposure to infection was therefore indubitable. Their ages varied from 1 month to 15 years when first seen. For purposes of comparison they were divided into 3 groups: (1) A group of 28 (tuberculin reactivity immaterial), who were vaccinated with BCG, 22 of them by injection and 6 orally. (2) A group of 32, tuberculin positive, who were not vaccinated with BCG. (3) A group of 23, tuberculin negative, who were not vaccinated with BCG. Of the first group 32 per cent developed leprosy, 8 of these being tuberculoid and 1 indeterminate. In the second group 41 per cent developed

leprosy, all but one indeterminate case being tuberculoid. In the third group 43 per cent developed leprosy, 5 being tuberculoid, 2 indeterminate, and 3 lepromatous. The significance occurs in the presence of the lepromatous cases in the third (tuberculin-negative group), as against their absence in the tuberculin-positive group. There is also a marked relationship between the positive Mitsuda reaction and the positive tuberculin reaction in the first two groups. The author concludes that if BCG is effective in the prevention of leprosy, and if vaccination by mouth is innocuous, he would advise mass oral vaccination of the people in an endemic area but, failing this, priority should be given to lepromin-negative contacts with open leprosy.

I. G. Ignacio, C. A. Palafox and F. A. José write on *The Results of Repeated Lepromin Testing in Children.*

Fifty small children of leprous parents in the Culion Leprosarium had with one exception been separated from their parents at birth, the exception being a child who had been exposed to contact with his mother for some hours. The lepromin reaction was tested four times, twice in 1949 and twice in 1950. A fifth test was made in 1951, but only in 32 of the children. A final test was made in December, 1951, about 2¼ years after the first trial, in the 47 children still available. In the first test only 22 per cent were positive. In the third test 96 per cent reacted. In the fourth all reacted, many of them reacting intensely although less than a year old. After the sixth lepromin test there remained 12 children whose reaction had not passed the 2+ grade. Ten of these who had negative tuberculin reactions were vaccinated with BCG in April and July, 1952, using the multiple puncture technique. When the lepromin test was done a seventh time, 2 months later, the reaction had not increased from 2+ in any of the 10 children.

Experimental Vaccination with BCG in the Prophylaxis of Leprosy is the subject of a paper by R. Chaussinand.

In order to test the effect of BCG vaccination in the prophylaxis of leprosy, two methods may be used: (1) Oral vaccination of 50 per cent of all new-born children comparable as regards age and sex, the remaining 50 per cent being used as controls. (The vaccinated and controls would be comparable as regards age and sex.) (2) Vaccination intradermally with BCG, using only those non-reactive to lepromin and to heat-killed virulent Koch bacilli. While important results might be obtained by the former method, the latter is preferable, as those affected by Koch's bacillus and

most of those affected by Hansen's bacillus would be eliminated. In order still more to eliminate those previously affected by the latter bacillus, only infections (excepting those in the new-born) that appeared more than 3 years after the beginning of the experiment should be taken into account. It is also regarded as likely that intradermal administration of BCG would be more effective than oral because the leprosy bacillus has a particular affinity for the skin; and this is confirmed by experiments in guinea-pigs, where with equal doses of BCG the intradermal route gives rise to more marked reactivity to lepromin than intraperitoneal vaccination. Detailed statistical analysis of the results would be made.

F. Amendola describes the profound difference in *eyes, nose and throat complications* of leprosy since the introduction of sulphone therapy. Formerly Pinkerton writing of the Hawaiian Islands said: " all patients sooner or later are affected with ocular complications." To the specialist the incipient invasion of the episclera always heralded " frank lepromatous involvement and certain blindness." With sulphone treatment, leprosy of the eye is now limited to invasion which occurred before sulphone therapy was begun. Surgery of the eye in patients treated with sulphones offers a better chance of restoring the transparent media. In the State of São Paulo 235 tracheotomies were performed for lepromatous obstruction of the air passages between 1933 and 1948; between then and 1955 none have been necessary.

S. G. Browne gives the results of treatment of 67 patients with *Sulfon-cilag.* The types of disease were: 57 lepromatous, 9 tuberculoid and one indeterminate. Chemically, it is the sodium salt of 4-carboxymethylamino-4'-aminodiphenyl sulfone, and it is freely soluble in water. It was administered in tablet form. The dose was 200 mgm. thrice a week, but varied with the size and condition of the patient. Later, doses of 100 to 200 mgm. were given daily. The results are shown in tabular form after 12 to over 36 weeks' treatment. All the tuberculoid cases progressed towards complete healing. " Lepromatous cases showed, in the main, both clinical and bacteriological improvement during the period of treatment. . . . It suggests that if therapy could be continued for longer than was possible in the cases under review, it would result in both bacteriological and clinical amelioration."

S. Schujman took a group of 40 cases of tuberculoid leprosy, 28 of them strong reactors to lepromin and 12 weak reactors. He made simultaneous *lepromin tests with diluted and undiluted antigens.*

With the integral (Mitsuda) antigen the strengths were 1 : 20, 1 : 100, and 1 : 750; with Dharmendra's bacillary antigen they were 1 : 1,000 and 1 : 5,000. It was found that with strong reactors the reactions were similar, but a little weaker with the more dilute antigens; while with the weaker reactors there were often no reactions with the higher dilutions. It is recommended that high dilutions should be used only in patients who have already been found to be strong reactors.

H. Floch, because of the difficulty in obtaining sufficient suitable material for preparing *lepromin antigen*, used a 1 in 750 dilution. To enhance the strength of the reaction 12 per cent glycerine and 2 per cent paraffin were added to the diluted antigen. This addition increased the strength of the reaction in 50 per cent out of 114 cases. The reaction was less in only 9. A 50 : 50 mixture of a 1 in 375 diluted antigen with a 1 in 20 normal skin suspension gave stronger results in 76 per cent of 79 positive reactions.

R. Kooij writes on *The Value of the Histological Criterion for the Classification of Leprosy.*

With a view to testing this, skin sections from 45 cases of leprosy were sent to 7 different pathologists for reports. Of these 45 cases, 9 were classified clinically as lepromatous, 18 as border-line and 18 as tuberculoid. There were 33 reports of the 9 lepromatous patients, but only 12 of these were diagnosed as lepromatous, 8 being tuberculoid, 6 mixed, and 7 non-specific. For the 18 border-line cases there were 87 reports, giving 18 lepromatous, 26 mixed, 21 tuberculoid, and 22 non-specific. For the tuberculoid specimens there were 77 reports, 37 giving tuberculoid, 16 mixed, 22 non-specific and 2 lepromatous. It is concluded: (1) That different cases of the same type of group may show different histological pictures. (2) That investigators differed in their opinions on the same section. (3) That one cannot exclude the diagnosis of leprosy on finding a non-specific histological picture. (4) That when the histological picture is not in agreement with the classification based on other criteria, one does not neecssarily have to change the classification. (5) That agreement of the histology with the clinical criteria of a definite type or group of leprosy gives support, and should be helpful in doubtful cases.

A Bridge of Compassion, by A. Donald Miller. 150 pp. 1955.

This is the title of a book published by the Mission to Lepers and written by its General Secretary, Mr. A. D. Miller. The work

of the Mission is the Bridge of Compassion, and it is described as having three arches: those of physical healing, human fellowship and eternal hope.

First is described the origin of the Mission from small beginnings some 80 years ago. Now " its work extends to twenty-four countries. It acts in co-operation with forty-nine missionary societies and the churches that have been established through them; it sees with gratitude the changing attitudes of Governments and peoples from paralysed fear or indifference to constructive reasonable service."

Under the " Arch of Physical Healing " are described the great advances that have been made in the treatment of leprosy in recent years, so that even in the advanced stages of the disease recovery can be expected.

Then there is the " Arch of Human Fellowship." The inter-denominational nature of the Mission, and the common appeal which this cause makes to all Christians of whatever denomination, creates a fellowship which bridges across all minor differences.

The third is the " Arch of Eternal Hope." Many interesting stories are gleaned from Mr. Miller's recent tours in Africa, India and the Far East. But the sad tale is also told of the plight of post-war Korea, where leprosy is one of the most urgent problems.

The last chapter speaks of the " Bridge Beyond." An island leprosarium in Japan is described where a small but increasing number of patients are Christians. The pastor, himself a patient, described their Church as " a fellowship which began with thirty members when the church was built. Now we are over a hundred. Soon the church will not be large enough to hold us. The message of Christ is drawing in other patients and its influence spreads through the whole leprosarium."

The final paragraph speaks of the Latin Vulgate version of Isaiah's record about the Messiah: *"Nos vidimus eum quasi leprosum"* (We beheld Him as leprous). " Yet in that tortured and despised body flowed the very life of God for man."

REPORTS

The International Congress at Rome

Dr. E. Muir represented the Mission to Lepers and the British Empire Leprosy Relief Association at the International Congress held at Rome from April 16th to 18th, 1956. The Congress was organised by the Sovereign Military Order of Malta to consider the " Relief and Social Rehabilitation of Persons suffering from

Leprosy." Some 250 delegates were present from 52 different countries.

The moving spirit was M. Raoul Follereau, who had presented the disabilities of those suffering from leprosy in such a way as to rouse the keen interest of the Order. Several scientific papers were read at the Congress but they chiefly had a bearing on the main theme.

Before the opening session the Congress members were invited to the Vatican, where the Pope gave a well-informed and sympathetic address on leprosy, and the duty of Christians to do everything possible to alleviate the sufferings of its victims.

The Sovereign Military Order of Malta has an interesting history. It began as the Hospitallers of St. John of Jerusalem, who served the pilgrims visiting the holy sites. Later they became military so as to protect the pilgrims from robbers, and were called upon by the Christian King of Jerusalem to protect the Holy Land. Under Moslem pressure they went to Cyprus, then to Rhodes where they became a Sovereign State. Later they went to Malta. For centuries they were one of the chief bulwarks against the widespread advance of Islam. In more modern times they were conquered by Napoleon, and the Order was finally transferred to Rome. Now, no longer with sovereign or military objectives, they are engaged in the relief of suffering in many countries of the world, and have recently taken a particular interest in leprosy.

The Resolutions passed by the Congress were as follows:—

The International Congress for the Relief and Social Rehabilitation of Persons suffering from Leprosy, meeting in Rome under the sponsorship of the Sovereign Military Order of Malta from the 16th to the 18th of April, 1956, comprising 250 delegates from 51 nations, considering that leprosy is a disease of low contagiousness and amenable to treatment,

RESOLVES

I. (a) That patients afflicted with the disease be treated as are those suffering from other infectious diseases, tuberculosis for example, without any other special regulations whatsoever; and that, in consequence, all discriminatory laws should be abolished.

(b) That in countries where leprosy is a problem, carefully planned propaganda measures should be taken to promote public understanding of the true nature of leprosy and to remove all prejudices and superstitions associated with the disease.

II. (a) That measures be adopted for early discovery and treatment of cases. Patients should be left at home provided that the state of their disease does not constitute a danger to their associates; this should have an important favourable psychological effect.

(b) That in countries where economic and medical resources are inadequate, but where endemicity is high, a mass treatment campaign be undertaken to control the disease; hospitalization should be limited to those whose condition requires special medical and/or surgical treatment and should terminate when such treatment is completed.

(c) That children be protected from infection by every approved biological means. Removal to a preventorium should be resorted to only in cases of absolute necessity because of the distressing stigma attached to residence in such institutions.

(d) That governments be encouraged to grant to those seriously disabled the moral, social and medical assistance necessary for their protection and rehabilitation, through the agency of various governmental departments, such as social welfare, agriculture and education, which will have a beneficial psychological effect both on the patients and on the public.

The Itu Leper Colony, Nigeria. Report for 1955.

[The following are abstracts from this most interesting report.—Ed.]

It is now twenty-eight years since the first group of patients came into the forest near Itu town and began to build.

The two big dates in the medical year in the Colony fall in July and December, when the half-yearly discharge of patients takes place. The announcement of these big days is eagerly awaited. In July, 1955, 315 names were called out, and at the end of December, 286.

It was with very great regret that we said good-bye to Miss W. E. Attoe, our first BELRA nursing sister, towards the end of the year. The death of her father made Miss Attoe's return to England necessary, and home affairs have made it impossible for her to come back in the meantime.

Much of the smooth running of the farms and general work of the Colony depends on what is called " Distribution." Distribution occurs every Thursday at 7 a.m. and preparations for it are made by the BELRA Agriculturalist on the previous day. For farm and town work the patients are divided into strong and weak companies of some ten to twelve men or women. The working week begins on Thursday.

It is always a pleasure to take officers of the Agriculture Department to the livestock farm. The keeping of livestock in Eastern Nigeria is seldom done on a large scale, and the eyes of the officers light up as they breathe deeply of the almost forgotten odour of the farmyard. During the dry season the pasture is poor, but the long grass which grows on the rice fields in the off-season is cut and brought in to supplement the feed. The stock has increased to over a hundred cattle and some fifty sheep.

During the year conversations have taken place with the Director of Agriculture in an effort to make the Colony not only a centre for leprosy healing but secondarily a place for recognised training in farming. The large majority of the patients come from farm work and will go back in a year or two to the same work. The Department of Agriculture are anxious to demonstrate and teach improved methods of farming, and also of co-operation in farming. The Colony has all the facilities for such training. It is hoped that the Department may be able to approve a scheme of training, and enable an African agricultural officer to be appointed to the Colony staff. It is our hope also that the Nigeria Leprosy Service will co-operate by encouraging men and women patients in other areas to come to Itu and benefit by the facilities which will be afforded here.

The Chief of the Colony, Mr. Isaac Obianwu, has given the information for the report on the general administration for the year. Mr. Obianwu, who entered the Colony in 1932 as a small boy, must know the Colony and its people better than anyone else. It was nineteen years before he was discharged symptom-free, and he was the obvious choice for the post of Chief. A town council or local court is part of the life of all citizens of this country, and the early decision of the doctor to leave as much as possible of the conduct of the affairs of the people of the Colony in the hands of the patients themselves was a wise one. The Chief is President of the Court, which meets once a week. All the language groups in the Colony are represented in its membership. The cases dealt with are many and varied, and the fact that appeals against court decisions to the Administrative Superintendent are few, is evidence that justice is truly meted out.

Research Unit and Owerri Area Annual Reports, Nigeria Leprosy Service, 1955. (An Abstract.)

SULPHONE TREATMENT

1. There is still no evidence among our patients of the development of drug resistance to sulphones. This is a remarkable fact.

2. Response to DDS, both clinical and bacteriological, in general gives the appearance of actually improving, as an increasing proportion of patients are attending while the disease is still in its early stages. Our experience is that the more early the infection, the more rapidly is it controlled by sulphones. Early lepromatous cases do not exhibit the long period usual in advanced cases, during which bacilli in small numbers continue to persist after the spectacular reduction in numbers seen during the first two years.

3. Sulphone treatment must be continued for a long period. No case should have treatment for less than two years, and in many patients considerably longer periods are necessary.

4. Patients on a steady daily dose of 100 mg. DDS are less liable to suffer from neuritis during treatment than patients receiving 300 or 400 mg. twice weekly.

The observation of these patients has to include their follow up after discharge. Patients discharged from treatment have been examined periodically in large numbers and records maintained.

EPIDEMIOLOGY

The extensive records available here now provide a valuable source of information relating to the epidemiology of leprosy of this area. Interest has centred on two aspects:

1. The decline in leprosy now evident and widespread which commenced before sulphone treatment became general, but has gained in momentum during the past three or four years. This has been examined in conjunction with other workers.

2. The incidence of leprosy among children born to women suffering from leprosy and receiving sulphone treatment, where no attempt has been made to separate child from mother. This study, now in progress, may yield some information as to the prophylactic value of DDS.

NERVE INVOLVEMENT IN LEPROSY

The prevention of deformity following nerve involvement is still one of the major problems confronting the leprologist, and although definite progress has followed the more detailed, and careful oversight of patients which is given generally nowadays, it is sometimes exceedingly difficult to arrest the inexorable develop- of paralysis which occurs in some patients in spite of all treatment. This subject merits more attention than we are able to give it at present.

One aspect of the problem relates to the treatment of trophic ulcers, and definite advance has followed the introduction of the walking plaster technique (*Lep. Rev.* **26**, 2). It has been used now in over 100 cases, and results on the whole have been very satisfactory.

The whole of Owerri Province is now effectively covered with leprosy treatment clinics, and, apart from one or two localities, facilities for isolating infective cases are adequate. The general

decline in the disease, evident for several years, now is gaining in momentum, its extent bearing a very close relationship as between one locality and another, to the degree of co-operation given by the people. On all sides there is evidence of the great importance of this as a factor in leprosy control. Where co-operation has been given freely, the disease is everywhere now at a low level, with few signs of present activity. Where co-operation has been defective, not only is the decline of the disease less apparent, but new infections persistently appear. The examples in Table I are of interest as indicating the change in the leprosy situation in localities where co-operation has been good.

Leprosy in Indonesia

In a population of 82 millions there are 26,000 registered leprosy patients, 5,000 of whom are in leprosaria, and 1,000 isolated in their own houses. There are eight full-time doctors and 109 qualified nurses.

Segregation is not obligatory in Indonesia, hence absconding of leprosy patients is no problem. In fact there are many patients who would like to enter the institutions, but who cannot be admitted for lack of accommodation, or money for their support. It is planned to establish an anti-leprosy campaign service in each province, for which purpose at least five leprosy doctors are needed, each with a full complement of assistants.

Patients admitted to leprosaria are mainly those patients suffering from lepromatous leprosy, all of whom should require segregation during their period of contagious activity. But there are many such who refuse admittance, because of the economic need to support their families.

> "Rehabilitation is not mere physical restoration attended by economic sufficiency in an environment which is removed from normal society. Rehabilitation is Restoration to Normal Life."

So said T. N. Jagadisan, Organising Secretary of "Hind Kusht Nivaran Sangh" (Leprosy Association of India). It is gladdening that a change for the better is noticeable in this respect, which is the fruitful result of the educational campaign of the Information Department of the Leprosy Service in Indonesia. There are already quite a number of leprosy patients allowed to continue their work as government officials and as employees in private enterprises while under medical treatment; also school children with leprosy of the negative type are at present allowed to attend school with due observance of the existing government regulations.

TABLE I

A. Leru Clinic, Owerri Province

	Year													
	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954
1. Total Patients on Treatment	103	172	197	220	243	300	306	330	300	204	113	94	82	65
2. New Admissions:														
(a) Total	103	107	56	36	31	80	26	34	33	19	7	13	12	14
(b) Lepromatous	32	21	21	9	7	15	4	8	2	8	1	—	—	2
(c) Children under 15	6	11	6	5	—	3	4	—	1	—	1	1	1	—

B. Ohafia Clinic, Owerri Province

	Year												
	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954
1. Total Patients on Treatment	256	287	443	440	454	419	402	310	245	123	100	79	81
2. New Admissions:													
(a) Total	256	72	204	48	29	82	43	38	34	41	22	11	17
(b) Lepromatous	37	13	18	7	3	9	5	7	6	6	3	3	1
(c) Children under 15	18	4	16	6	1	4	5	5	3	1	—	1	1

ABSTRACTS

BCG Vaccination in Pakistan

[In view of the possible value of BCG in the prophylaxis of leprosy, the following abstracts from **Chronicle of World Health Organisation,** Vol. 10, No. 5, may be of interest.—Ed.]

In August, 1949, the Government of Pakistan, with the assistance of the International Tuberculosis Campaign (ITC), started to carry out a professional training and demonstration project with the aim of familiarising Pakistani doctors and nurses with the technique of BCG vaccination. At the end of 1950, the programme was being applied in all the provinces of the country and was favourably received everywhere.

When the BCG programme was launched in 1949, practically nothing was known as regards the tuberculin sensitivity of Asian peoples, and it was decided to employ the same technique as that used for BCG campaigns in Europe. The Mantoux test was used for case-finding, i.e. the intradermal injection of 1 TU, followed by an injection of 10 TU in the event of a negative reaction. The reaction was considered positive if the induration measured 6 mm. or more in diameter three days after the injection. Only persons who reacted negatively to both 1 TU and 10 TU were selected for BCG vaccination. This method, which required three visits, was simplified as soon as the results obtained by the Tuberculosis Research Office (TRO) with single injections of 10 TU or 5 TU became known. A dose of 5 TU has been used since August, 1950. The Moropatch test, which was applied at the outset to children under 12 years of age, was given up after a few months for various reasons, in particular because it was less sensitive in the case of Pakistani children than the Montoux test.

At the 1951 census, the population of Pakistan was 76 million; 12 million inhabitants underwent the tuberculin test between August, 1949, and December, 1954. Nevertheless, only 9 million attended for the reading of the test, so that a quarter of the tests were carried out in vain. Four million, or slightly less than half the persons completing the test, gave no reaction; and almost all of them (99 per cent) have been vaccinated.

The age distribution of the persons tested is as follows: under 7 years of age, 21 per cent; 7-14 years, 29 per cent; 15-19 years, 15 per cent; 20 years or more, 35 per cent. The corresponding figures for persons vaccinated are 32, 36, 13 and 19 per cent. As can be seen, the vaccinated population is, on the whole, younger than the tested population. This is due to the fact that a relatively

high proportion of older persons reacted positively to tuberculin and consequently were not eligible for vaccination.

Tuberculin testing during mass campaigns can give an approximate idea of the prevalence of tuberculosis in a community. For this purpose, the population concerned should be divided into two separate groups,. the infected and the non-infected. It may be asked to what extent classification according to the diameter of the induration enables such a distinction to be made. It is impossible to say with absolute certainty whether a person with a 4 mm. or 5 mm. reaction belongs to one or the other group. In West Pakistan it was found, however, that these " doubtful " reactions constituted only 4 per cent of the total. In East Bengal medium-sized reactions are much more frequent than in West Pakistan, and the distribution of reactions according to the diameter seems to indicate the presence of two types of tuberculin sensitivity; a high-grade sensitivity due to tuberculous infection and a low-grade non-specific sensitivity*. The presence of non-specific sensitivity (which has been observed, moreover, in other parts of the world) would seem to limit considerably the usefulness of the tubeculin test, since the largest non-specific reactions cannot be distinguished from the smallest specific reactions. In West Pakistan it is difficult to classify persons developing indurations of 4-5 mm. after the administration of a dose of 5 TU; in East Bengal the same problem arises for persons with reactions between 4 mm. and 10 mm., i.e. 40 per cent of the population tested.

In determining the prevalence of tuberculous infection on the basis of the number of persons found to be allergic to tuberculin, it was decided to exclude the figures for East Bengal, in view of the frequency of non-specific sensitivity in that province, as well as the data collected in the tuberculosis dispensaries and permanent BCG centres and during control tests.

Bearing these reservations in mind, the distribution of tuberculin-reactors of both sexes belonging to the age-groups 7-14 years and 15-19 years respectively, is as follows: 48 and 65 per cent in the provincial capitals, 45 and 52 per cent in the urban areas, 41 and 56 per cent in the rural areas. Allergy is generally more frequent among young men of 15-19 years than among girls of the same age. As to children aged 7-14 years, the study has revealed a very interesting fact, namely, that in the large towns the percentage of positive reactors is higher among boys than among

* Can this be partly the result of infection with leprosy which is much more common in East than in West Pakistan?—Ed.

girls, while in the other urban areas it is almost equal for both sexes, and in the rural areas it is higher among girls than among boys.

Treatment of Ulcer of the Foot, by Rev. C. C. Pande and Dr. J. N. Banerjee, Bankura Leprosy Home.

With simple dressings and rest of the foot, chronic foot ulcers may heal within six or eight weeks, where there is no underlying dead bone. Shoes are used with a packing of sawdust and rubber solution paste in the sole of the shoe to prevent pressure at the ulcer points on the sole of the foot. The shoes give comfort and check development of the ulcer, as long as the sawdust paste remains spongy. This paste slowly becomes hard, but remains good for 3 to 4 months. As it is expensive to supply a patient with shoes two or three times a year, simple dressings were tried and found very satisfactory.

On 7.10.55 six patients (three male and three female) with ulcer of the foot were selected. Two had very bad anaemic superficial ulcers. The margins of the ulcers were cleaned and dead tissue was removed. The ulcer was rubbed with methylated spirit and dressed daily with lint soaked in 5 per cent aqueous solution of sulphetrone. Two patients who had oedema and slight discharge at the beginning were given magnesium sulphate baths for a week, which cured the discharge.

The patients' movements were restricted. The area of the ulcers began to diminish from the third week, and by the seventh week all the ulcers had healed. One patient, the oldest of the six, did not restrict his movements and had small ulcers in two places. All the patients are now allowed moderate walking and to date (February, 1956) no ulcers have recurred.

*** Trop. Dis. Bull., Vol. 53, No. 1, Jan. 1956**

An Attempt to Control Leprosy by BCG Vaccine in the Loyalty Islands, by **Lacour.** 1955. Noumea, New Caledonia: South Pacific Commission.

The Loyalty Islands were considered particularly suitable for the trial because of the stability and homogeneity of its population, and because there was already accurate knowledge of leprosy and detailed records of annual case-finding. The total population is 12,612. Leprosy entered the islands in 1880 when a teacher

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returned from Guama (Maré) infected with the disease. In 1899 there were 125 cases on Maré, 60 to 80 on Lifou, and in 1924 there was an index of 5.39 per cent on Ouvea. In 1953 the census gave 338 on the three islands, and in October 1954 there were 319, of which 98 were considered contageous and were isolated, the remaining 221 were placed under medical supervision in the villages.

The operational work was the lepromin test on the 1st day, recording the lepromin test and doing the tuberculin test on the 21st day, recording the tuberculin test and BCG vaccination (if necessary) on the 25th day. Preliminary BCG vaccination had been contemplated but was abandoned for lack of staff. The BCG vaccine used was dry frozen BCG from the Pasteur Institute, Paris. It was applied in parallel skin scarifications made through drops of vaccine suspension applied to the forearm. The vaccine had to travel over sea, a 30 to 36-hour trip, in thermos flasks, but was found on culture to show no loss of vitality.

Work was begun on Maré Island and, after a two days' survey, 2,639 of the 3,602 inhabitants were lepromin tested and 2,611 tuberculin tested. Some inhabitants were absent fishing and on other employment: 1,321 were vaccinated with BCG. Similar work was done on the other islands.

The tuberculin, lepromin and other indices are given in tabular form. During the next years an attempt will be made to control and maintain tuberculin allergy, study Mitsuda reaction, test those not seen originally and the newly-born, and study carefully all new cases of leprosy through clinical, immunological and bacteriological procedures.

Study of the Staining of Acid-fast Bacilli with Sudan Black, by **R. Chaussinand** and **M. Viette.** Ann. Inst. Pasteur. 1955, Sept., Vol. 89, No. 3, 28089.

The authors describe a method of staining acid-fast bacilli with Sudan black in alcoholic solution, and decolourising with acetone, then contrast staining with Pyronine or Safranine. With this tubercle bacilli are stained black, leprosy bacilli are not stained at all, rat leprosy bacilli gray, paratuberculous bacilli different shades from black to Safranine. The *Myco. marianum* was stained more or less like the paratuberculous bacilli. It is hoped to use this method for classifying acid-fast bacilli.

Is it Possible to Reinforce the Positivity of Mitsuda Reactions Brought about with Dilute Antigens without Losing the Specificity of their Response? by **H. Floch.** Bull. Soc. Path. Exot. 1955, Vol. 48, No. 3, 372-5.

Using a Mitsuda antigen of 1/750 dilution it was found, upon comparing the results with this alone and those when 2 per cent of liquid paraffin and 12 per cent of glycerine were added, that of 102 tests 42 were the same, in 9 the supplemented antigen were inferior, and in 51 it was superior to the unsupplemented. In 12 the reaction was negative with both antigens. It is therefore concluded that the diluted antigen effect is enhanced without the specificity of the reaction disappearing.

Can Vaccination with Myco. marianum be used in the Prophylaxis and Treatment of Leprosy? by **R. Chaussinand** and **M. Viette.** Rev. Coloniale de Med. et Chir. 1955, Vol. 27, No. 238, 158-62.

Three suspensions of acid-fast bacilli killed by heat, B. fleole, Myco. marianum, and BCG, were injected, each into six guinea-pigs. After the third injection they were all submitted to the lepromin test. There were 4 reactions with Myco. marianum, and 5 with BCG, and the sizes of the nodules produced were considerably larger with BCG. It is therefore considered that this is evidence that BCG is superior to Myco. marianum in the prophylaxis of leprosy, especially as the former can be used alive.

*** Trop. Dis. Bull., Vol. 53, No. 2, Feb. 1956**

Six Months Treatment of Leprosy in South Vietnam with 4,4' Diamino-diphenyl Sulphoxide and 4,4' Diethyloxythiocarbanilide, by **N. P. Buu-Hoi, Nguyen-Ba-Khuyen** and **Nguyen-Dat-Xuong.** Bull. Acad. Nat. Med. 1955, Vol. 139, Nos. 15/16, 275-80.

The former of these drugs (styled DDSO for short) was tested for six months on 34 patients, of whom one was of the indeterminate type, 6 were of the lepromatous type, and 27 mixed [no definition is given of this term.] The daily dosage was 0.1 gm. given orally from the beginning of treatment and continued throughout. In 19 of these the treatment effects were watched throughout, and in 13 there was more or less marked improvement clinically. In 2 cases the skin smears became negative, and in 14 the nasal smears

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became negative. There were no toxic symptoms, and there were no reactions except in 2 patients in which it was evanescent and soon disappeared when they were put on reduced doses of 0.05 gm.

The second of these drugs (styled " dialide " for short) was tested on 13 patients, of whom 2 were indeterminate and 11 mixed. The dosage was the same as for DDSO. There was clinical improvement in 11 patients, all signs almost disappearing in one and nearly so in another. Thickening of nerves quickly became less. In 2 patients an eczematous rash came out all over the body and treatment had to be stopped. In 2 patients the skin smears became negative and in 11 the nose smear became negative.

Later, a group of 300 patients living at home has been treated with dialide, and they have stood the treatment well, except for a few who had eczematous eruptions at the beginning of treatment, which disappeared when the dosage was reduced. In all these the improvement was similar to that in the former group. The authors consider that the nasal smears became negative more quickly than under treatment with other drugs.

May we use Vaccination with Myco. marianum in Prophylaxis and Treatment? by **R. Chaussinand** and **M. Viette.** Bull. Acad. Nat. Med. 1955, Vol. 139, Nos. 7/8, 165-9.

The only justification for the use of a vaccine prepared from Myco. marianum would be if it produced a stronger sensibility to lepromin than does BCG, and the authors have shown by comparative trials that it does not do this. This organism belongs to a vast ill-defined group of mycobacteria known as paratuberclous, many members of which group have been tested in the treatment of leprosy, but never with any beneficial results. It would, therefore, not be right to deprive leprosy patients of the value of sulphones in order to test the questionable therapeutic effects of Myco. marianum.

Bacteriological Interpretation of Skin Smears and Biopsies in Leprosy, by **D. S. Ridley.** Trans. Roy. Soc. Trop. Med. 1955, Vol. 49, p. 449.

It was found in histological studies of leprosy patients, 11 in number, that the result of treatment did not at first diminish the density of bacilli in the leproma, but led to invasion of the leproma by the surrounding healthy corium, while the uninvaded portion remained densely bacteriologically positive. In this way many nodules disappear during the early stages of the treatment. It is

considered that serial biopsies at 2-month intervals, and using improved methods of staining sections, give a more accurate estimate of improvement under treatment, though multiple smears provide a more rigorous test of cure.

Isoniazid with Sulphones in Lepromatous Leprosy, by **W. H. Jopling** and **D. S. Ridley.** Trans. Roy. Soc. Trop. Med. 1955, Vol. 49, p. 453.

Four batches of lepromatous (one was border-line) patients were tested, 3 on sulphones, 3 on sulphones with isoniazid, 3 received the combined treatment followed by sulphones alone, and 2 received sulphones followed by combined treatment. The result failed to establish an advantage for either of the 2 types of treatment at the end of 2 years. The only side effect of isoniazid was an elevation of the glucose tolerance curve, followed by a return to normal after the cessation of treatment.

Radiological Bone Changes and Angiographic Findings in Leprosy, by **D. E. Paterson.** Journal of the Faculty of Radiologists, 1955, Vol. 7, No. 1, 35-46.

A study has been made of 542 films from 116 selected patients. Bone changes are divided into: bone destruction, joint changes, bone absorption, and osteoporosis. Bone destruction may be local and in the form of " cysts " due to foci of lepra bacilli, especially when lepra reaction occurs. A destructive lesion in the medulla may cause expanded cortex similar to tuberculous dactylitis. Joint changes are commonly the result of infection with lepra bacilli in the subarticular bone. But bone destruction is most commonly connected with injury resulting from the diminution or absence of sensation. The patient fails to take precautions after such injury and secondary infection enters then spreads to the bone.

Bone absorption is shown by radioscopic evidence to be evenly and smoothly removed from the ends or from the subperiosteal layers of the bone. The author does not believe that this change, which was found in 97 of the 108 cases, can be termed " atrophic," for it is found in other diseases such as acute osteitis, periostitis and osteomyelitis in which there is not neural involvement.

By using angiograms, after intra-arterial injection of diodone, studies were made of the vessels of the fingers. Digital arteries were found to be narrowed in badly deformed fingers of leprosy in a way similar to what is found in rheumatoid arthritis, but this may be due to want of use or to former non-specific infection.

Evidence is quoted for the theory that bone formation and destruction can be caused by nervous stimuli. " Where there is a nerve lesion it is known that trophic changes take place in the skin. In sensory loss there is absence of normal reflex stimuli that may well influence the mechanism of tissue repair and replacement. There may well be a similar reflex nervous mechanism controlling the balance between osteoclasts and osteoblasts. There is no evidence, however, that the bone changes in leprosy are *primarily* due to loss of such a nervous mechanism. It is also shown that the type of concentric " atrophy " seen in leprosy, tabes and syringomyelia can also occur in mycetoma and non-specific ulceration where there is no disease of the nervous system. " It is thought that in cases of concentric absorption there is occlusion of the vascular end-loops in the soft tissue and in the periosteum as a result of periostitis, haematomas, or devitalised tissue. Blood supply to the periosteum is therefore affected in such a way that osteoclasts rather than osteoblasts are at work. The vascular end-loops and the veins draining the medulla may be protected from this process, and so in the medulla compensatory new-bone formation can take place."

The article is illustrated with 35 figures.

The Medical Problems of Easter Island, by **G. Roberto.** Rev. Med. de Valparaiso, 1954, Sept., Vol. 7, No. 3, 302-9.

This little island, nearly 1,900 miles to the west of Caldera on the coast of Chili, has an area of about 69 square miles. It was annexed by Chile in 1888. The population does not exceed 800. The chief sanitary problem of the island is leprosy, which is supposed to have been brought by Polynesians, originally from China. In 1952 there were 34 leprosy patients (12 women and 22 men), 27 of whom were between 20 and 30 years of age. There is a leprosy hospital with 3 wards and 20 beds, and the condition of the patients is now very much better than it was 20 years ago. There are now 14 in the hospital, 21 on ambulatory treatment with DDS, and 17 under observation. There is no word of syphilis in the reports. Tuberculosis has not been introduced, and it is suggested that the inhabitants should be protected by BCG vaccination. Virus epidemics are often spread rapidly after the arrival of ships, the infection returning to the crew with increased virulence after spreading through the inhabitants.

* **Trop. Dis. Bull., Vol. 53, No. 4, Apr. 1956**

Serology in Leprosy: Antilipoid and Antisyphilitic Antibodies, by **G. Tarabini Castellani.** Rev. " Fontilles," Valencia, 1955, July, Vol. 3, No. 8, 572-7.

Serological tests were practised, using the sera of 20 leprous patients. All these sera were positive or partly positive to Bordet antigen and to the Meinicke, Kahn and Citocol tests. Using the Palida reaction (complement-fixation using an antigen derived from the treponema of Reiter) only 2 of the sera were positive and a third doubtful. From this it was concluded that only in those 2 (and doubtfully in a third) sera was there present antisyphilitic antigen, though in all of them there was antilipoid antigen.

* **Trop. Dis. Bull., Vol. 53, No. 5, May 1956**

Leprosy in the United States, by **L. F. Badger.** Pub. Health Rep. Wash. 1955, June, Vol. 70, No. 6, 525-35.

No nation-wide case-finding programme has ever been conducted in the United States to find out the prevalence of leprosy. The data in this paper are based on the records of patients admitted to the National Leprosarium at Carville from its opening in 1921 up to 1953. Patients were admitted from all but 8 of 50 States. Of the 1,465 admitted, 326 were from Louisiana, 324 from Texas, 294 from California, 158 from New York, and 102 from Florida. Of the 1,465 total, 822 were born in the continental United States, and 637 in foreign countries. A number of foreign-born persons in whom clinical leprosy developed after their arrival in the U.S. were not admitted to the leprosarium; thus of 248 cases in California who were born in Mexico, only 100 were admitted. Of 50 States, 15 are recorded as non-endemic, that is without records of patients being born in them, though 7 of these have sent patients born abroad to the leprosarium. " Of 158 patients admitted from New York, 140 were of foreign birth and only 18 were born within continental United States. Of the latter only 2 were born in New York." During the period 415 patients were admitted from non-endemic States and the District of Columbia. Of these, 288 were born outside continental U.S. and 126 were natives of the U.S., the birthplace of one was not known. Of 521 known cases in California, 436 were of foreign birth, 41 were born in other States, and only 34 were born in California, the birthplace of 10 are unknown. Not only is leprosy confined to a few States, but it is

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also confined to a limited area in each of these States. In Florida, cases were recognised among residents of only 11 of the 67 counties during the 33-year period, and of only 8 counties during the last 10 years. It has been concentrated in one country, Monroe, and within this county, in Key West. Of 96 Florida-born patients, 44·5 per cent resided in Key West at the time of diagnosis. Of the foreign-born patients admitted 100 were from Mexico, 52 from the West Indies, 49 from the Philippines, 28 from China, 23 from Greece, 18 from Italy, 10 from Russia, and 8 from Spain. Nearly half of the patients admitted were admitted more than 5 years after the onset of the disease, and 17.5 per cent more than 10 years after onset, the period being considerably longer in the case of European-born patients than in patients born in the West Indies.

Leprosy: Pathological Changes observed in Fifty Consecutive Necropsies, by **C. S. Powell and L. L. Swan.** Amer. J. Path. 1955, Nov.-Dec., Vol. 31, No. 6, 1131-47.

Of the 50 cases necropsied, 2 were of the tuberculoid and 48 of the lepromatous type, the type most common in the Carville Leprosarium and in the United States. Changes of secondary amyloidosis were seen in 23 of the cases in one or more tissues, the organ most affected being the kidney. When the kidney was involved by amyloid change it was usually quite markedly altered. In 19 cases as a result, death was from renal insufficiency. Out of 49 spleens sectioned 8 contained miliary lepromas. In 3 cases amyloid change was prominent in the mucosa and submucosa of the stomach. The pancreas was not involved. Acid-fast organisms with lepromas were found in 5 of the 46 cases in which adrenal sections were available. In 16 of the adrenal glands sectioned, amyloid change was noted, principally between and replacing cords of cells in all three layers of the cortex. In 6 of the 32 bone marrows sectioned *Myco. leprae* was demonstrable in lepromas, and several of the more active cases with widespread miliary lesions had very hyperplastic bone marrow; a severe hypochromic microcytic anaemia was present in several cases. " The so-called ' burned out ' cases may reveal few or no organisms—one of the oldest patients in this series became blind from leprous changes in 1898, 8 years after the clinical onset of leprosy. He refused virtually all specific treatment except for sporadic doses of chaulmoogra oil approximately 1,000 cc. Several years prior to death, over 60 years after the onset of his leprosy, skin scrapings were positive only occasionally. No organisms were demonstrable at necropsy."

As seen by the average duration of life of 20 years after the recorded onset of obvious signs and symptoms, leprosy is not a fatal disease, and the average age at death is 59, less than 10 years below that of the population as a whole.

*** Trop. Dis. Bull., Vol. 53, No. 6, June 1956**

Findings in Leprosy and Tuberculosis with the Wassermann, Meinicke and VRDL Tests, by **H. Ruge.** Bull. World Health Organisation, Geneva, 1955, Vol. 13, No. 5, 861-86.

H. Ruge, writing on Serological Findings in Leprosy and Tuberculosis with the Wassermann, Meinicke and VDRL Tests, examined serologically in the course of a venereal disease survey in Egypt, 820 cases of leprosy and 720 cases of tuberculosis with the Wassermann, Meinicke (MKR II), and VDRL tests.

On serological and anamnestic evidence, 31 cases of syphilis were discovered among the leprosy cases and 37 among the tuberculosis cases. Apparently false positive reactions were seen in 203 cases of leprosy (25 per cent) and in 38 cases of tuberculosis (5 per cent). The author discusses the probability that a fairly high proportion of these reactions were in fact caused by otherwise undetected syphilis or were non-specific.

The Meinicke test proved the most specific of the three, followed, in that order, by the Wassermann and the VDRL tests.

It was found that syphilis was more frequent among males with tuberculosis than among those with leprosy; this is attributed to the fact that leprosy patients are kept in greater isolation. Less easily explicable is the fact that more females than males with leprosy were found to have syphilis, whereas in tuberculous persons the difference in syphilis incidence between male and female patients was not very great.

Treatment of Ulcerating Fissures and Leprous Perforating Ulcers with a Combination of Trichloracetic Acid and Salicylic Acid, by **L. Lauret** and **P. Kerbastard.** Méd. Trop. Marseilles, 1956, Jan.-Feb., Vol. 16, No. 1, 83-92.

Twenty per cent of patients at the Marchoux Institute for Leprosy suffer from trophic troubles of the extremities. There are deep fissures of the heel, toes and between the digits, occurring in both the dry and the wet weather. Perforating ulcers are the most frequent and intractable trophic lesions. Under good food and

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sulphone treatment patients make remarkable improvement, but the ulcers do not show equally favourable results.

The remedy tried was either a glycerine solution or a pomade of trichloracetic acid and salicylic acid (ATS), 3 per cent of the former and 0.5 per cent of the latter. Seventy leprosy patients with fissures of the feet were treated morning and evening for 10 minutes in baths containing the glycerine solution. Within 15 to 45 days all the fissures closed and the hyperkeratosis diminished, although the patients continued to cultivate their fields during treatment.

A second group of 39, with 8 who had fissures, 23 with perforating ulcers and 8 with other ulcers, were treated with poultices of ATS for 8 days, followed by the ATS pomade. Of the 42 perforating ulcers affecting the above 23 patients, 14 healed up, 10 improved and 4 improved slightly. Of 17 perforating ulcers treated by a combination of this method and daily intravenous injections of dycholium (dihydrocholate of sodium) 7 healed up, 5 were improved and 2 were slightly improved. The superior results from this combined treatment are attributed to the antiseptic and epithelium softening actions of the acids, and the vasodilatation of the bile salts.

Investigation of Tuberculosis in those suffering from Leprosy, by **J. J. Baldo.** Rev. Sanidad y Asistancia Social, Caracas, 1954, Sept.-Dec., Vol. 19, 5/6, 361-71.

The investigation was made in the patients of the Cabo Blanco Leprosarium, Venezuela. The patients had been examined for tuberculosis 12 years previously and were now re-examined. The tuberculin alergy showed in 709 leprous patients a high positivity, with an early incidence in the younger groups comparable with that found in those with poor economic and social standards outside the leprosarium. The positive percentage was rather lower in the second than in the former enquiry, but this could be accounted for by a difference in the Mantoux technique. Chest photography in 827 leprous patients, using first microfilms, and then 30 x 40 cm. films in those with abnormal appearances, followed by examining the sputum of those suspected of suffering from pulmonary tuberculosis, gave 10.7 per cent of pathological findings, compared with 21.2 per cent in the former examination. Those with early active tuberculosis were only 0.6 per cent compared with 3.2 per cent formerly; and those with more advanced disease only 2.0 per cent compared with 6.7 formerly. There is thus a marked decline in

the incidence of tuberculosis. This may be due partly to better hospital conditions, but the chief reason for the improvement is probably the effects of sulphone therapy, which improves the general health of the patients. The atypical trabecular and reticular shadows due to leprosy of the respiratory passages are also much less.

The Motor Unit in Leprous Neuritis. A Clinico-Pathological Study, **D. K. Dastur.** Neurology, Bombay, 1956, Jan.-March, Vol. 4, No. 1, 1-27.

Study of the literature leads the author to the conclusion that leprous neuritis is an ill-studied problem, though perhaps the commonest cause of muscle disorder in India. He studies: (1) the clinical features of sensory and motor loss, (2) terminal innervation of muscle by intravital staining, (3) changes in voluntary muscles, and (4) various "neuropathies." From 69 leprous patients 75 muscle biopsies were obtained, the *flexor carpi ulnaris* being chiefly used. A portion of an ulnar nerve was obtained at necropsy. Clinical study showed that "the zone of sensory loss was generally well defined and roughly corresponded to the anaesthetic areas resulting from peripheral nerve injuries."

The pathological changes found in the muscles were: reduction of the over-all density or even loss of innervation, beading or fragmentation of the nerve fibres, shrinkage of end-plates, prominence of Schwann nuclei, and proliferation of endoneurium and perineurium. Along with these signs of degeneration there were regenerative signs such as collateral branching and formation of growth cones and end-plates. In some cases there were signs of inflammatory myositis. Rarely acid-fast bacilli were found in intramuscular nerve twigs or connective tissue. There was evidence that muscular atrophy and degeneration of end-plates preceded changes in motor nerve fibres, and the neuritic process was slow, giving time for diagnosis and treatment. The role of anatomical and mechanical forces in determining the degree of disease in infected nerves is discussed, as are also the effects of pressure and ischaemia in first causing blocking and then progressing to necrosis.

[There is much valuable information in this paper, which should be read in the original.]

Preliminary Note on the Preparation of a Standardised Lepromin, by **R. Chaussinand, M. Viette** and **R. O. Prudhomme.** Bull. Soc. Path. Exot. 1955, Vol. 48, No. 6, 784-8.

The objections to the lepromin antigen prepared according to Wade's method by filtration through nylon are that an amount of tissue debris remains, and that the bacilli are gathered together in masses or globi. This massing of bacilli is an even greater disadvantage when it is sought to dilute the antigen, both as a measure of economy and with a view to testing the degree of sensitivity to the antigen. Grinding up with glass powder is not suitable, as this does not dissociate the masses sufficiently and fine particles of glass are left in the suspension. Two methods have been found to give promising results. (1) Treatment of Wade's antigen with 1 per cent papain, raising the temperature to 70° during 5 minutes, keeping it at 70° for 5 minutes, and boiling for 5 minutes. It was found that when this was filtered through nylon about a third of the tissue debris had been eliminated. (2) Ultra-sonic action was used to dissociate the bacilli in a suspension of Stefansky's bacillus. With a freqency of 960 kilohertz and 90 watts applied for 15 minutes there was a diminution in the number and size of the masses. In 3½ hours the majority of the masses were dispersed, but a few small ones persisted, but the number of the bacilli seemed to have diminished. Using a lepra bacillary suspension with a similar method applied for 4 hours, and examining a drop of the suspension every 15 minutes, it was found that after 30 minutes the number of the globi had diminished, but the number of single bacilli was the same. By 45 minutes the bacilli had diminished by half. By 4 hours there were very few masses and globi, and very few isolated bacilli. There was thus much less resistance of Hansen's bacilli to supra-sonic vibrations than of Stefanski's bacilli. Using this 4-hour treated suspension of lepra bacilli to test patients, the early reaction was slightly stronger than with the ordinary antigen, and the delayed reaction practically identical with it. However, in lepromatous cases a slight local reaction was noted which lasted for a few weeks. Attempts were made to find out if this latter was due to the partly broken up tissue debris or to the supra-sonic treatment of the bacilli. It was observed that the injection of the supernatant fluid, after centrifuging the treated antigen for half an hour, produced no local reaction in allergic patients.

It was found that the papain-treated antigen does not give any false positive reactions, but is rich in bacilli. It is hoped by combining the two methods to produce a reasonably homogeneous antigen suitable for dilution.

Treatment of Lepra Reaction with Phenylbutazone, by **Drs. P. Destomes** and **L. Chambon.** Bull Soc. Path. Exot. 1955, Vol. 48, No. 4, 454-8.

Following the work of Ravina and Pastel in acute inflammatory conditions in tuberculosis, the authors tried derivatives of pyrazolidine. Five patients suffering from lepra reaction were given six intramuscular injections of 5 cc. of 20 per cent solution of phenylbutazone, one every three days for three patients, and two courses of three daily doses with an interval of two days between the two courses for two of them. Five other patients were given orally in tablet form 300 to 400 mgm. daily for seven to nine days.

The results were found to be at least as good as those obtained with ACTH and more lasting. First of all, pain disappeared generally within 24 hours, and this was followed by the fever subsiding and the reduction of inflammation of skin and nerve lesions. One of the patients was of the tuberculoid type, though the histological picture was at first obscured by the reaction, and appeared to be lepromatous. However, 12 days after the fourth injection the histological picture had changed to be typically tuberculoid. Swelling of the prominent swollen nerves was quickly reduced. Slight traces of albumen were found in the urine, but these were transient and not considered as contraindications. There was also aqueous rentention and oedema occasionally, but this quickly passed off. In only one case was there a return of reaction after treatment was finished, and this quickly subsided when the treatment was renewed. Phenylbutazone has another advantage over ACTH in that it is much less expensive.