LEPROSY REVIEW

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LEPROSY REVIEW

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Editorial

I NEW FORMAT

This is the very first issue of the new format which we have adopted for *Leprosy Review*, and we wish to acknowledge with thanks the help and skill of our printers, Messrs Eyre and Spottiswoode Limited, The Queen's Printers. The main aim behind choosing the new format is to secure greater readability. We have also been thinking of the many authors who write original articles for *Leprosy Review* and, incidentally, this new format has given more latitude in the number of papers which can be published in any one issue. We hope that the readers and authors will like the result of the new format.

2 THERAPEUTICS OF LEPROSY

In the previous issue we devoted the main attention to the surgical side of leprosy with a written symposium from many authors on Plantar Ulcer. This time we return to a subject which in modern times is also a constant preoccupation, that is, the search for possible drug improvements. This issue contains reports on two drugs which are of intense interest. (a) B 663 - On this drug we have papers by Barry and Conalty on the antimycobacterial activity; Browne on the possible anti-inflammatory action in lepromatous leprosy, appraisal of the pilot trial after three years, and red and black pigmentation developing during treatment. It will be found that these will repay careful study.

(b) Isoxyl - Another drug which will attract attention is Isoxyl on which Griffiths has given a preliminary report.

In conjunction with B 663 it is worth while noting that the book by V. C. Barry on Chemotherapy of Tuberculosis is reviewed on page 49.

Another valuable report is by Browne on injectable thiambutosine (Ciba 1906).

There are other articles of interest such as by Lennox on the surgical management of foot deformities; Browne on varicelliform eruption appearing in the course of acute exacerbation; and Banerjee and Roy on an electrophoretic study of leprosy serum.

The Antimycobacterial Activity of B 663

VINCENT C. BARRY and MICHAEL L. CONALTY

Laboratories of the Medical Research Council of Ireland, Trinity College, Dublin

B 663 is one of a large series of rimino-compounds of structure 1 synthesized originally in these laboratories as potential antimycobacterial agents. These are orange-red phenazine derivatives whose colour is related to their quinoneimine character. In B 663, R" represents \cdot CH(CH₃)₂ and R' and R" are \cdot C₆H₄Cl(p) residues. The synthesis and chemistry of these compounds have been described by Barry and co-workers in a series of papers (1956a, 1956b, 1956c, 1956d, 1958a, 1958b, 1959, 1962b).

The forerunner of these compounds, anilinoaposafranine (I, R'' = H, R' = R''' = Ph), had been shown to be highly inhibitory of the growth of tubercle bacilli (H37Rv) *in vitro* (Barry *et al* 1948). It had also shown activity in mouse and guinea-pig tuberculosis (Barry 1951; Conalty 1951; Barry *et al* 1956e) and in human renal disease (Lane 1951). Allday and Barnes (1952) used it with some success in leprosy patients in Nigeria.



B 663 (1. $R'' = CH(CH_3)_2$ is a crystalline material insoluble in water but highly soluble in fat. Its inhibitory activity as determined by our methods (Conalty 1954) against H₃₇Rv and a number of atypical mycobacteria is shown in Table I.

Mice

In murine tuberculosis B 663 is extraordinarily active (Barry *et al* 1957). At the low dose of 1 mg./kg. bodyweight in the diet for 14 days, beginning on the day of infection with the bovine Ravenel Rv strain, B 663 produces a significant extension of survival time. Again, mice which received 1 mg. each of B 663 intraperitoneally *once* only, on the 11th day of an infection which

Mycobacterium	Concentration causing complete inhibition of growth (μ g./ml.)		
Myco. tuberculosis, H37Rv includ- ing wild, isoniazid-resistant, streptomycin-resistant and PAS- resistant strains	1.3-3.3		
Myco. bovis, Ravenel Rv, wild and drug-resistant strains. Also BCG	1.3-3.3		
Myco. avium, three strains	5.0-10.0		
'Unclassified' Mycobacteria <i>Myco. kansasii</i> , two strains Scolochromogens, two strains Battey types, 10 strains Runyon Group <i>IV</i>	3.3–5.0 3.3–5.0 1.0–6.6 6.6–20.0		
Myco. ulcerans**	2.0		

TABLE I Antimycobacterial Activity of B 663 in vitro*

*Proskauer and Beck medium enriched with human serum, 5 per cent. Incubation for 14 days. **Incubated at 32°C.

caused the death of untreated mice in 19 days, had a median survival time (MST) of 79 days. Perhaps its most striking property is its genuine prophylaxis against tuberculous infection. Thus mice which were fed at the level of 10 mg./kg. in the diet for 14 days and then taken off treatment, were afforded a considerable degree of protection when challenged with the usual lethal intravenous infection with Ravenel Rv four weeks later (Barry and Conalty 1958). In established disease (treatment from the sixth day of infection) B 663 orally (5 mg./kg.) for 14 days effectively reverses the disease process. Further confirmatory reports on the activity of B 663 in murine tuberculosis have been published from other laboratories (Hirsch 1958; Vischer *et al* 1958; Noufflard and Berteaux 1955a and 1958b; Acharya *et al* 1959; Grumbach 1960; Drabkina and Ginsburg 1962). The drug is also fully active against strains resistant to isoniazid, streptomycin. PAS or thiosemicarbazones.

Syrian hamster

Vischer *et al* (1958) showed that B 663 exerted good curative properties in experimental tuberculosis of the hamster and in this animal also, a striking prophylactic effect could be demonstrated.

Guinea-pigs

The therapeutic activity of the drug in guineapig tuberculosis was much less impressive. Thus although when administered at a dosage level of 140 mg./kg. for 79 days, treatment beginning on the 21st day of infection, the disease index was reduced from 44 to 8.5, the disease being confined to the site of infection and the adjoining lymph nodes (Barry *et al* 1957), at lower dosage levels the results were disappointing. B 663 at 20 mg./ kg. in the diet from the 21st day of infection produced a 50 per cent extension in MST and notably less lung disease in the treated animals. Vischer *et al* (1958), Steenken *et al* (1960) and Drabkina and Ginsberg (1962) also reported unimpressive results in this animal species.

Rabbits

In established disease experiments in rabbits, Freerksen observed a good therapeutic effect with oral doses of 50 mg./kg./day.

Monkeys

As with the guinea-pig, results of treatment in the monkey were also disappointing. Schmidt (1959) administered B 663 by stomach tube to infected monkeys. At 10 mg./kg./day there was some effect and at 100 mg./kg./day the effect was marked when treatment was initiated at the time of infection. When, however, treatment was withheld for 30 days after infection, the drug even at the larger dosage level failed completely to hold the disease. Bacilli recovered from the treated monkeys at autopsy were reported to have a reduced susceptibility to B 663.

In vitro resistance

Under our conditions, growth of the human

H37Rv and the bovine Ravenel strains of Myco. tuberculosis (0.03 mg. inocula) in Proskauer and Beck medium, to which 5 per cent human serum is added, is normally inhibited by 1.3 to 3.3 μ g./ml. B 663. To study the development of resistance to B 663 the procedure adopted was to set up serial dilutions of the drug $(I\frac{1}{2} \text{ fold steps})$ and inoculate with 0.03 mg. of tubercle bacilli. After two to six weeks incubation, such growth, in the tubes of the highest concentration of drug, as was adequate in amount, was used as inocula for further series. The procedure was repeated at two to six weeks intervals. Under these conditions, 15 successive subcultures produced no change in susceptibility although the total exposure to B 663 was 80 weeks. In other experiments employing 10 fold inocula of the Ravenel strain slight growth was evident at 100 μ g./ml. in the fourth serial culture and growth was as heavy as in the control tubes at this concentration of B 663 after the 14th subculture or a total exposure time of 71 weeks. With the H37Rv strain under these same conditions the fifth serial culture showed some growth in the presence of 50 μ g./ml.

The Ravenel strain which was now growing freely (large inoculum) at 100 μ g./ml. of B 663 also grew freely at this concentration when the usual small (0.03 mg.) inocula were employed. When given to mice in the standard intravenous inocula (0.1 mg.) it proved to be still moderately virulent despite the long period of subculturing – all dead at 66 days with a MST of 28 days. A group of 10 mice also infected in this way but treated for 14 days with B 663 in the diet (20 mg./kg.) had a median survival time of 120 days, only one mouse dying within 95 days. These cannot be considered resistant bacilli.

In vivo resistance

Mme Grumbach (1960) has isolated variants of H37Rv from mice treated for three and four months at a dosage level of 1 mg./mouse/day. These bacilli were much less susceptible to B 663 *in vitro* and it needed five to ten times the dose of drug to control infections produced by them in mice.

Schmidt also isolated bacilli of reduced susceptibility from monkeys treated with B 663 (100 mg./kg./day) for five months. One of these variants which we studied had a very low virulence in mice. It was reisolated after four months from mice which had been treated for 14 days with B 663 (5 mg./kg.) and still showed reduced susceptibility *in vitro*. Inoculated again into mice it had now fully recovered its virulence but responded to treatment with B 663 (20 mg./ kg.). The same variant kept on subculture in Lowenstein slopes for 18 months fully recovered its susceptibility to B 663 *in vitro*, its virulence for mice and also its susceptibility in the mouse to treatment with B 663.

An observation of great interest which we have made and which has been confirmed by Grumbach (1961) is that tubercle bacilli which have emerged from *in vitro* studies or in the mouse and monkey and which exhibit a reduced susceptibility to B 663 are still susceptible to other rimino-compounds, *e.g.* B 749 (I, R'=R'''= *para*chlorophenyl; $R''=N\cdot CH_2\cdot CH_2NEt_2$). This phenomenon is being studied further.

Bacilli resistant to isoniazid or ethionamide can be developed readily in a few subcultures in a tween-free medium enriched by serum. We have shown that if sub-inhibitory concentrations (e.g. $0.5 \,\mu g./ml.$) of B 663 are present, no change in susceptibility of H37Rv to isoniazid could be demonstrated after ten successive titrations extending over a period of 17 months. In a series of experiments in mice infected with the H₃₇Rv strain of Myco. tuberculosis, Grumbach (1960) has shown that, under treatment with B 663 (16 to 20 mg./kg.) or isoniazid (4 to 5 mg./kg.) or ethionamide (40 to 50 mg./kg.), the bacillary count in the lungs falls rapidly until about the 65th day and then in each case begins to rise rapidly again. This is the well-known 'fall and rise' phenomenon associated with the development of drug-resistant bacilli. When, however, B 663 was combined with isoniazid or ethionamide, at the dosage levels mentioned, the bacillary count continued to fall, reaching almost zero in 150 days, and no resistant bacilli appeared. Vischer and Roulet (1963) also found that B 663 delayed the emergence of isoniazid resistant strains in mice.

Absorption, distribution and retention

The genuine chemoprophylaxis of B 663 against experimental tuberculosis referred to earlier makes the pharmacology of this substance of great interest (Barry *et al* 1959b, 1960). As ordinarily presented in powder form, B 663 on ingestion is absorbed in amounts adequate to exert high antituberculosis activity in the mouse, hamster and rabbit. It is also well absorbed in the rat. Blood levels attainable in the guineapig are very low and in man 90 per cent of the drug presented in this state is excreted unchanged in the faeces. To counter this poor absorption in man the drug has been prepared in micronized form by Dr E. Hodel, Geigy Pharma, Basle.

In mice B 663, whether given as a powder or in micronized form, is well absorbed. At the end of 28 days treatment with B 663 (25 mg./kg.) in the diet, the lungs contained approximately 800 μ g./g., the spleen 4,000 μ g./g., the fat 800 μ g./g. and the plasma 3.0 μ g./ml. Twentyone days off treatment reduced these values to 60 (lungs), 85 (spleen), 350 (fat) and 1.1 (plasma). Higher dosage or extended periods of treatment had little effect on the plasma level.

In rats treated at the high level of 100 mg./ kg./day in the diet, plasma levels reached 8μ g./ml. and lung levels, 1,000 μ g./g.

Guinea-pigs on a dose of 20 mg./kg. continued for 30 days proved to have 140 μ g./g. of drug in the lungs but even at the end of this period plasma levels never reached even 1 μ g./ml. At the end of 326 days treatment (50 mg./kg. in the diet) the plasma level was still little more than 1 μ g./ml. although the lung tissue contained 18,500 μ g./g.

In man when the drug is given orally in the micronized form 70 to 90 per cent is absorbed and serum levels on a dosage of 600 mg. per day reach 3 to 4 μ g./ml.; skin and lymph node may contain 40 μ g./g. (Knight 1964). Excretion is slow and some colour may be seen in the urine many weeks after cessation of treatment.

Reticulo-endothelial system

The low plasma and high tissue levels of B 663 which can be reached in different animal species are due to the active take up of the drug by the cells of the reticulo-endothelial system (Conalty and Jackson 1962a, 1962b). This phenomenon has so far been most studied in mice. When mice are treated at the rate of 50 mg./kg. (in the diet), in three to four days orange-red rounded bodies, 1 to 2μ diameter, appear in the cytoplasm of macrophages. On continuing treatment bright red crystals are seen accompanying the round inclusions (seven

to ten days) and at the end of a few weeks most of the cells contain crystals only. The above sequence of events is particularly well seen in the mesenteric lymph nodes and in the spleen. The appearance of crystals in the lung macrophages is somewhat delayed. Macrophages already loaded with crystals continue to take up carbon particles and tubercle bacilli. B 749, the analogue of B 663 referred to earlier, does not colour the fat in mice and appears even on prolonged treatment as a diffuse colouring of the cytoplasm and is never seen in crystalline form.

Apart from fat cells, B 663 is only noticeable in macrophages; its retention for long periods in these cells probably favours its therapeutic effect but its rapid withdrawal from the blood makes it difficult to establish or maintain therapeutic levels in some animal species. We had thought for this reason that another rimino-compound more soluble in aqueous media, e.g. B 749 also highly effective in mice, might produce higher blood-levels and thus show a better effect in, for example, the guinea-pig. Unexpectedly, however, we found that although B 749 does not accumulate to any extent in fat, it builds up very quickly in the solid tissues. So effective is the uptake of this drug by the macrophages that it has not been possible to obtain blood levels even as high as those obtained with B 663 treatment. Accordingly it is much less active than B 663 in guinea-pig tuberculosis.

The distribution of B 663 in the animal after ingestion, resulting in high concentrations in certain organs and low levels in the blood, throws some light on its therapeutic effect in different animal species. Thus it is very effective in the mouse and hamster where the bacilli tend to be intracellular and poor in the guinea-pig where the bacilli are for the most part extracellular. This is not the whole story, however; we know that B 663 is present at a very low level in the plasma in mice when an impressive prophylaxis can be demonstrated. It has been suggested that the binding and transport of the drug by serum proteins may be different in the mouse and guinea-pig. Binding to lipoprotein in the serum of mice is, however, complete and yet the therapeutic effect of the drug is excellent in this animal (Buggle). The nature of the lesions in experimental tuberculosis in different species is obviously of great importance.

Murine leprosy

In view of the intracellular location of B 663 in macrophages its examination in leprosy was clearly indicated. Chang (1962) states that 'B 663 has emerged as the most active drug yet tested in the treatment of murine leprosy'. It is the first drug to hold the infection in check for 816 days although the infection was not eradicated. Of various combinations of several antituberculosis drugs, the combination of B 663 and isoniazid was apparently the only one which caused an actual reduction of the established infection. There was evidence that in mice treated with this combination, Myco. lepraemurium acquires some degree of resistance to isoniazid but not to B 663. Shepard (1963), emplying his mouse footpad technique, has shown that 0.1 per cent B 663 in the diet causes complete suppression of growth of human leprosy bacilli.

Experience in man

The first trial of B 663 in human leprosy was carried out by Browne and Hogerzeil (1962a, 1962b, 1962c) who reported that B 663 had a definite action in lepromatous leprosy, inducing clinical and bacteriological improvement. No signs of toxicity were noticed over a 12 month period. A preliminary small scale trial has also been completed in Kuala Lumpur with encouraging results (Rees 1964). Knight and his associates at the National Institutes of Health, Bethesda are conducting a very thorough examination of the behaviour of B 663 in a small number of leprosy patients (Knight 1964). Much more extensive clinical investigation of B 663 in leprosy has now been planned or is already under way in Nigeria, Malaya and elsewhere (Rees 1964) and when the resulting reports appear it will be possible to assess more completely the status of B 663 as an antileprosy drug.

Other mycobacterial infections

The report (Lunn and Rees 1964) of the successful treatment of mycobacterial skin ulcers, due to atypical mycobacteria resembling *Myco. ulcerans*, in Uganda with B 663 has aroused considerable interest. These authors also reported that B 663 showed a very high activity against three strains of Uganda mycobacteria, three strains of *Myco. ulcerans* and two freshly isolated strains from Australia. Standardized infections in the foot-pads of mice produced by these strains of mycobacteria were completely suppressed by 0.006 per cent of B 663 in the diet. This report has already led others to consider the possibility of exploiting B 663 in a variety of mycobacterial infections in man.

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'B 663' Possible Anti-inflammatory Action in Lepromatous Leprosy

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In the course of the clinical trial of 'B 663' (Geigy, S.A.) see Barry, V.C., Conalty, M.L. 1965 Leprosy Review, this issue reported by Browne and Hogerzeil (1962a, b), it was noted that only two out of the 26 participating patients suffering from lepromatous leprosy developed any symptoms of acute exacerbation while receiving the drug, and in both instances the attack was slight and transient and occurred during the first month of treatment. It is a well-attested observation that in any group of patients suffering from lepromatous leprosy of comparable severity and receiving dapsone in standard doses for a similar period, a much higher proportion would have developed some degree of acute exacerbation. Of the 26 patients, 21 had B 663 for six months, and the remaining five for 12 months: 13 patients received B 663 alone, nine together with dapsone and four with dapsone and ditophal.

(Two patients suffering from bacteriologically positive borderline leprosy are excluded from consideration here, since they are not subject to the same type of acute exacerbation as are patients with lepromatous leprosy. As a matter of interest, however, it may be recorded that neither had any kind of exacerbation during treatment with B 663, but that one of them subsequently developed an acute ulnar neuritis.)

Acute exacerbation on subsequent dapsone therapy

That this group of 26 patients with lepromatous leprosy is typical in respect of liability to exacerbation is shown by the fact that after dapsone had been substituted for B 663, 14 of them developed erythema nodosum leprosum (ENL) and various other manifestations of acute exacerbation. In addition, some patients showed certain features that are frequently though not necessarily associated with such a state; thus, three had acute polyneuritis, one had severe bilateral dactylitis, and one passed through an acute psychotic episode. It should be added that one patient succumbed to pneumonia during the 13th month of treatment for leprosy.

In the 14 patients affected, the sign of ENL appeared first at various intervals after the change-over to dapsone therpay. In no patient did ENL lesions appear until seven months had elapsed after B 663 therapy had been discontinued. Thus, they appeared after eight to 12 months in five patients; after 13 to 18 months in three; after 19 to 24 months in five, and during the 29th month in one.

To summarize: during treatment with B 663, two patients developed ENL during 186 patient/ months (*i.e.* five patients for 12 months, and 21 patients for six months); no patient developed ENL after the first month of such treatment, *i.e.* in 160 patient/months. During treatment with dapsone, 13 patients developed ENL during the next 589 patient/months (*i.e.* 24 patients for 24 months, plus one patient developed ENL after 29 months.

The two patients who had experienced a transient attack of ENL during the first month of B 663 treatment did not develop any ENL lesions when subsequently taking dapsone.

As in other reported series, there was no constant correlation between the appearance of ENL and the absolute height of the Bacterial Index, or its increase or decrease, or changes in the proportion of normal-staining bacilli (the Morphological Index).

The occurrence of bacterial 'resistance' in five patients after 12 months of B 663 therapy alone, as shown by a more or less sudden increase in the Bacterial Index and the simultaneous reappearance of normal solid-staining rods in the smears at several sites (Browne and Hogerzeil 1962 c.), seemed to have no bearing on the incidence of acute exacerbation.

Influence of total dose of B 663

There was no evidence that the five patients who had received B 663 for 12 months were less liable to experience acute exacerbation than the 21 who had received the drug for six months, or that in them the onset of acute exacerbation was postponed by the additional amount of drug they had received. Three of these five experienced ENL of the same severity as the patients who had received the drug for only six months, and the time of onset appeared to be similarly fortuitous.

Clinical features of acute exacerbation

There was nothing in the clinical features of the acute exacerbation in these patients to distinguish them from the general run of such cases in West Africa (Browne 1963). All grades of severity were noted, from the slight and transient, accompanied by no systemic disturbance, to the severe and persistent, characterized by high temperature, general malaise, polyarthralgia, polyadenitis and widespread neuritis in addition to the cutaneous signs of superficial erythema nodosum and deep diffuse panniculitis. Iritis and iridocyclitis were not observed. Three patients had a single short attack, which cleared up either spontaneously within a month, or during temporary withdrawal of dapsone. In three patients, the first attack was more severe, and persisted for from five to 14 months. Ten patients had recurrent attacks spread over 30 months. In one patient in whom the acute exacerbation persisted for 14 months, the skin of the lower part of the posterior aspect of the arms became hard, dark, shiny and tender part of the picture of progressive lepra reaction.

In spite of the occurrence of ENL in these patients, and the consequent short or prolonged interruption of treatment in many instances, their overall clinical and bacteriological progress has been eminently satisfactory.

DISCUSSION

The incidence and pattern of ENL in this group of 26 patients (reduced to 25 by death) with lepromatous leprosy under treatment with standard doses of dapsone are in keeping with experiences of similar groups in West Africa. The interest lies in the virtual absence of acute exacerbation during previous treatment with B 663, whether or not another drug was being Since the pathogenesis of acute exacerbation in lepromatous leprosy is still obscure, it is idle at this juncture to speculate on the precise mechanism of B 663 in suppressing the phenomenon.

It is worth recording, however, that the disappearance of morphologically normal bacilli from the skin smears was proceeding at a very satisfactory rate during administration of B 663, and that disintegrating bacilli were present in an ever-increasing proportion of the bacillary load in the dermis and nasal mucosa.

It was not possible, because supplies of the drug were exhausted, to observe the effect of readministration of B 663 on patients who had developed acute exacerbation. Any sustained benefit that might be noted on the established condition would support the suggestion here advanced that B 663 appears somehow to exert a suppressive action on the development of acute exacerbation in lepromatous leprosy.

If it could be shown that patients with lepromatous leprosy under prolonged treatment with B 663, with perhaps the addition of dapsone, make rapid clinical and bacteriological progress and are spared the distress and risks of more or less prolonged episodes of acute exacerbation, with accompanying polyneuritis and ocular complications, then B 663 may well prove to be a drug with a definite and extensive sphere of usefulness in leprosy.

SUMMARY

Erythema nodosum leprosum occurred in only two out of 26 patients whilst they were undergoing treatment for lepromatous leprosy with B 663 (Geigy), and in both cases the condition occurred within the first four weeks of treatment and was slight and transient. When all the patients were subsequently given standard doses of dapsone, however, 14 of them passed through episodes of erythema nodosum leprosum whose clinical features corresponded with those observed in similar groups. It is suggested that B 663 (Geigy) may exert a suppressive effect on the development of acute exacerbation in lepromatous leprosy.

ACKNOWLEDGEMENTS

Thanks are expressed to Messrs J. R. Geigy, S.A., for supplies of B 663, and to Dr S. O. Egwuatu, Chief Medical Officer, Ministry of Health, Eastern Nigeria, for permission to publish this article.

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Treatment of Leprosy with B 663 Appraisal of the Pilot Trial after three years

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The preliminary and supplementary reports of the pilot trial of B 663 conducted at Uzuakoli (Browne and Hogerzeil 1962 a, b and c) offered evidence that the drug is active in human leprosy and that its action is probably enhanced by the addition of dapsone.

The present report summarizes the subsequent progress of the same group of patients three years after they had begun six or 12 months' treatment with B 663. (Some of them have now been under observation for four years.)

The patients

The patients, unselected and untreated, were placed on treatment in the order of admission. Of the total of 28, 26 had lepromatous leprosy and the remaining two had borderline leprosy highly positive bacteriologically. One patient died during the 13th month from a disease unconnected with leprosy.

Treatment

1. Twenty-two patients had six months' treatment with B 663; during this period:

Seven had no other drug;

ten had standard doses of dapsone;

five had standard doses of dapsone, together with ditophal (Etisul, I.C.I.) initially for three months.

2. Five patients had 12 months' treatment with B 663 alone.

At the end of the period of treatment with B 663, patients in all groups received standard doses of dapsone.

Dose/body-weight

Twenty patients whose body-weight averaged 118 lb. (53.6 kg.) received 300 mg. B 663 daily, or 5.6 mg. per kg. body-weight.

Seven patients whose body-weight averaged $87\frac{1}{2}$ lb. (39.7 kg.) received 200 mg. B 663 daily,

or 5.0 mg. per kg. body-weight.

One patient weighing 50 lb. (22.7 kg.) received 100 mg. B 663 daily, or 4.4 mg. per kg. body/weight.

The weight of drug given daily per kg. ranged from 4.4 mg. to 6.8 mg.

Results

To supplement earlier published reports, the following assessment was made at the end of the 36th month, counting from the beginning of treatment with B 663.

Clinical

All patients in all groups showed marked objective improvement, but no significant differences could be detected between the groups. From examination principally of the skin lesions (nodules, macules, diffuse infiltration) and peripheral nerves, the improvement was assessed as follows: excellent 20, very good 6, good 1.

Skin lesions

The degree of permanent macroscopic damage to the skin was proportional to the extent and more especially to the depth of the initial involvement. Young nodules and recently developed macular areas healed without visible trace, but lesions of long standing healed with obvious fibrosis and atrophy of the elastic subcutaneous tissue.

Nerve lesions

The slight nerve involvement seen early in lepromatous leprosy proved to be clinically reversible, but contractures and paralyses due to permanent nerve damage were unaffected by treatment with B 663. Some of the patients did not present themselves for treatment until probably three to five years after the clinically recognizable onset of the disease, when clawing, peripheral sensory impairment and neuropathic ulceration had already made their appearance; in point of fact, it was frequently these complications that brought the patients to the Diagnostic Clinic. It is reasonable to infer that the rapidity of action of B 663, alone or in conjunction with dapsone, coupled with the absence of acute exacerbation (including erythema nodosum leprosum and polyneuritic episodes) during treatment with B 663, prevented the nerve damage that would be expected to occur in such a group under other standard therapeutic regimes. Similarly, the development of iritis and iridocyclitis was probably forestalled.

Skin pigmentation

In the course of treatment, the skin became initially red and subsequently blackish. These changes were symptomless, and apparently without pathological significance. The red colour disappeared generally within six months of cessation of treatment with B 663, but the hyperpigmentation persisted for rather longer. Both the red and the black coloration might prove unacceptable in the lighter-hued, but the dark-skinned patients in this trial raised no objections.

Bacteriological

Normal-staining solid rods of M. leprae disappeared from the routine skin smears taken regularly from eight sites in skin and nasal mucosa between the 28th and the 52nd weeks, the disappearance being most rapid in the group taking B 663 and dapsone. The initial average percentage of normal-staining bacilli (42-52) was approximately the same for all groups.

An analysis based on the dosage of B 663/body-weight ratio showed no appreciable difference in the time necessary for complete disappearance of normal-staining forms between the high, medium and low dose/body-weight ratios, *i.e.* the speed did not seem to vary with the concentration of B 663. Analysed in this fashion, the average time taken lay between 32 and 38 weeks. In 15 patients with a high (*i.e.* over 51) initial Morphological Index (*i.e.* percentage of normally staining forms), the Index fell to zero in an average of 36 weeks, whereas in the remaining 12 patients, whose

ner standard a transient phenomenon, the excess myco-

32 weeks.

of M. leprae

bacterial load (accounted for by the solidstaining rods) gradually disappearing in the course of three or four months. The eventual bacteriological and clinical improvement in these patients seemed unaffected by this episode.

average Index was 24, the Index fell to zero in

The more or less sudden reappearance of a

varying proportion of solid-staining rods (of

M. leprae) at some or all the eight sites routinely

smeared, accompanied generally by a rise in the

Bacterial Index, after 12 months' treatment with

B 663 alone (Browne and Hogerzeil 1962 c) was

Reappearance of morphologically normal forms

Bacterial clearance

It is evident that the speed of removal of effete bacilli depends on factors unconnected with the bactericidal or bacteriostatic action of a drug that is apparently active in human leprosy. Apart from three patients suffering from exacerbation (developing during treatment with dapsone), no patient at the 36th month had a Bacterial Index of 0.5 or over (maximum: 4.0); in the 12 patients with a positive Index, the bacilli were very degenerate. In the remaining 15, no acid-fast material could be seen in any of the eight smears taken at monthly intervals by a standard technique.

The speed of clearance in the patients of the group that had been given dapsone in addition to B 663 was slightly greater than that of the others. No differences were noted between the patients on high, medium or low B 663/body-weight ratios.

The consistent and continuous decrease in the Bacterial Index in all groups was a gratifying feature of the treatment given.

Possible anti-inflammatory action of B 663

It was observed that while taking B 663, the patients appeared much less liable to experience episodes of acute exacerbation, though subsequent experience when they were receiving standard doses of dapsone indicates that as a group they were typically liable to such episodes. It seems possible that in these circumstances B 663 exerts a positive suppressive or antiinflammatory action.

HISTOLOGY

The improvement under therapy was consistent and rapid.

Sections taken before treatment showed lepromatous leprosy of a degree consistent with the clinical findings.

Within eight months, the numbers of foamy cells decreased considerably, to be replaced by a granulomatous infiltrate composed mainly of histiocytes. A noteworthy feature in several sections was the scanty character of this infiltration. *Pari passu*, the amount of collagen in the dermis increased.

The nerves were, typically, uninvolved in the cellular response; in many of them *M. leprae* could be seen, either singly or in groups lying between the nerve fibres.

Bacilli soon began to show gross morphological changes. Within six to eight months, all were fragmented, including those within the dermal nerve fibrils, and a high proportion had disappeared.

The conclusion reached on the histological appearances was that the response to treatment was very satisfactory. The typical lepromatous picture was rapidly modified, coming to resemble that of indeterminate leprosy.

Patients' reactions

Without exception, the patients taking B 663 are enthusiastic about the drug. Many other patients, having noted the progress of their fellows in this trial, have asked to be given the drug.

CONCLUSIONS

This group of patient with severe bacilliferous leprosy improved more consistently and more rapidly than any similar group in the writer's experience.

In the doses given, B 663 has an undoubted action in lepromatous and borderline leprosy, leading to relatively rapid clinical and bacteriological improvement.

While taking the drug, patients seem to be much less liable to episodes of acute exacerbation. Consistent with the rapid improvement, the risk of nerve and eye damage appears to be reduced.

The red coloration of the skin and the subsequent hyperpigmentation are transitory and symptomless phenomena of no pathological significance, and did not constitute a contraindication among the more deeply pigmented patients participating in this trial.

Since improvement was equally noticeable in patients having relatively low doses in relation to body-weight, it may be that doses smaller than those used in this trial may suffice to ensure clinical improvement and bacteriological progress, and at the same time still obviate acute exacerbation.

Attempts should be made to prevent the emergence of resistant forms by giving another drug in addition to B 663, such as dapsone, or isoniazid, as advocated by Chang (1962). The additive effect may accelerate not only the rate of disappearance of normal-staining forms but also the clearance of non-viable and fragmented bacilli.

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Red and Black Pigmentation developing during Treatment of Leprosy with 'B 663'

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The changes in skin colour remarked during treatment with B 663 of patients with lepromatous (26) or borderline (2) leprosy, have been briefly referred to in published reports (Browne and Hogerzeil 1962 a, b). This paper records in greater detail certain features both of the ruddiness and of the black coloration. Apart from the obvious bearing of this pigmentation on the acceptability of B 663, its development presents features of some pathological interest.

It is known from animal experiments that the safranin dyes in general stain the tissues yellow or orange or red, and the *aposafranine*, B 663 (2 - p - chloroanilino - 5 - p - chlorophenyl - 3:5 - dihydro-3-isopropyliminophenazine) is no exception, as Barry and his co-workers have pointed out in their series of carefully-documented papers (Barry*et al.*1957, 1960; Conalty and Jackson 1962a, b; etc.). Allday and Barnes had earlier (1952) reported that another safranin dye, B 283, coloured the skin of leprosy patients red and rendered the urine port-wine in colour; they attributed the latter to a metabolite of anilino-*aposafranine*(B 283).

In addition to the ruddiness of the tissues, (orange subcutis, pink small intestine, red fur), Chang (1962) noted a dark-blue coloration, 'resembling cyanosis', of the hairless areas (*i.e.* mouth, ears, tail and lower limbs), which appeared in all animals treated for nine months with B 663. The longer the treatment was continued, the deeper the coloration became: its appearance could be postponed or its intensity diminished by the concurrent administration of isoniazid. Conalty and Jackson (1962 a) also noted that the skin of their animals, initially pink from the accumulation of B 663 in the tissues, gradually became purplish black as treatment was continued.

THE RED COLORATION

The skin of all the 28 deeply-pigmented Nigerian

patients receiving B 663 developed some degree of ruddiness, the intensity of which was initially obscured to some extent by the depth of natural pigmentation.

Onset

In some of the lighter-hued patients, slight ruddiness could be detected as early as the tenth day of treatment. In all, it was definitely appreciable early in the second month. With a wide range of natural pigmentation and the gradual appearance of the redness, it was not possible to correlate either the appearance of detectable ruddiness or its subsequent intensity with the dose/body-weight ratio.

Clinical features

One patient complained of slight skin irritation preceding the ruddiness, but had no accompanying eruption, papular, macular or urticarial. Some patients had some feeling of tension in the succulent infiltrated lesions on the face. Otherwise, the coloration developed without symptoms. The patients volunteered that they experienced a sense of well-being.

The redness was first apparent and subsequently most noticeable in the thin, soft, hairless skin of the face (*i.e.* the peri-orbital and peri-nasal regions particularly) and the thick, hairless, hypopigmented skin of the palms and soles. Afterwards, the entire skin of the lighterhued could be seen to be ruddy. The conjunctivae were only slightly affected, as was the buccal mucosa.

Lepromatous lesions, including discrete lepromatous nodules and diffusely infiltrated skin, were not affected noticeably more than adjacent skin.

The ruddiness deepened while B 663 was being taken, *i.e.* for six or 12 months. It began gradually to disappear after the drug was stopped. The speed of disappearance varied between individual patients. In general, its intensity decreased during the second month after treatment with B 663 ceased, but the periorbital skin remained somewhat redder than normal for some months.

There was some red staining of undergarments and bedding, which could be minimized by a daily bath.

Urinary findings

The urine was deep red throughout this period, but no other abnormality, chemical or cellular, could be detected in it by the usual methods of examination.

THE BLACK COLORATION

During the second and third months of treatment with B 663, all the patients developed some degree of darkening of the skin, particularly of the discrete and diffuse leprosy lesions, but in many patients the entire skin eventually became affected.

A precocious indication of this change was the appearance of a circumscribed area of hyperpigmentation corresponding to the elastoplastcovered site of a biopsy incision. Patch tests for picric acid (which had been used for sterilizing the skin) and for elastoplast were both moderately positive, and the areas tested became hyperpigmented following a localized papular dermatitis. The entire skin of this patient subsequently became very dark.

Clinical features

The blackish-brown or purplish-black coloration deepened rapidly, and persisted unchanged for several weeks after cessation of treatment with B 663.

On the face, which was generally affected more than the trunk, it was the sites that were diffusely infiltrated or nodulated that became hyperpigmented most rapidly. The prominent areas, such as the superciliary ridges, the cheeks, the nose-tip, the chin, and the ears became darker than the rest of the face in several instances, whether or not they were the seat of obvious lepromatous infiltration.

On the trunk and limbs, the darkening was generalized, diffuse and symmetrical. Discrete lesions were usually, but not invariably, picked out by the hyperpigmentation. In the two patients with borderline leprosy, the skin just beyond the limits of the lesions was darker and more purplish than either the lesion itself or the surrounding skin. In some patients, the dorsa of the hands, and to a less extent the dorsa of the feet, became much darker than the rest of the skin. In one patient, the dorsal skin in the neighbourhood of the interphalangeal and metacarpophalangeal joints became black; in another the left hand was much blacker than the right; in yet another, one side of the nose was blacker than the other.

The conjunctivae, formerly but slightly pink, became muddy, and irregularly and diffusely pigmented.

As the leprosy lesions responded to the drug, the nodules became smaller, to be eventually replaced by scar tissue, recognizable as shiny circular macules, jet black in colour.

The black coloration persisted longer after the drug was stopped than did the redness. After the lapse of two years, it had disappeared in all but two patients, who were by nature deeply pigmented.

During its gradual disappearance, the dark coloration persisted in some patients as circumscribed hyperpigmented areas reminiscent of the elements of a dapsone-induced fixed eruption (Browne 1959, 1964) or the post-inflammatory hypermelanotic staining following lesions of erythema nodosum leprosum (Browne 1963).

A baby (aged 15 months, and still breast-fed) of the first patient to be treated with B 663, became ruddy like its mother, and subsequently developed a generalized darkening of the skin. Both the ruddiness and the darkening disappeared completely. (This child had some hazy patches of the trunk and face while the mother was taking B 663. No *M. leprae* were found in smears taken from the lesions, but their appearance resembled the abacillary prelepromatous macules not uncommon in West Africa.)

The skin of a baby born by Caesarean section of a mother who had received six months' treatment with B 663 together with dapsone (the last dose of B 663 having been given six weeks before delivery), was generally pinkish at birth, and became deeply red within a few weeks. The mother's milk was decidedly yelloworange in colour. The child's skin then became blackish brown, that is, much darker than would be expected in comparison with the degree of pigmentation of the parents' skin. The reddish coloration was noticeable in the periorbital skin for about six months after birth, but the hyperpigmentation persisted for nearly two years before finally disappearing.

HISTOLOGY

The red coloration

Specimens of skin removed under local anaesthetic and embedded and processed in the usual way, appeared to be generally and diffusely stained a bright pink - as with eosin. Examination of sections showed that the subcutaneous fat was more deeply stained than the dermis or epidermis. In preparations fixed and cleared secundum artem, no microcrystals of B 663 were visible and no 'ghosts' left by dissolved crystals could be discerned in sections of ordinary thickness. In frozen sections, however, Shepard (1964) has noted some accumulation of crystals in the liver of mice on very high drug intake, with foci of macrophages in and around the crystals. Some macrophages may actually contain the dye (Chang, 1964). These findings are in accord with the earlier experimental work of Barry et al (1959).

The black coloration

Specimens of skin removed at a latter stage, when it was becoming black to the naked eye, revealed a varying microscopic pattern that could be generally correlated with the clinical appearances.

At first, there was a reduplication of the stratum germinativum, with a consequent increase both in the number of strata of pigment-bearing cells and in the density of the pigment.

Later, single cells and then groups of elongated melanocytes in the stratum germinativum could be seen to have ruptured on their deep aspects, releasing their melanin content into the papillary layer of the dermis. Amorphous masses of melanin of varying dimensions were not only scattered in the papillary layer (especially between the rete pegs) but were also seen lying free and surrounded by lymphocytes in the reticular layer. In some cases, amorphous melanin was distributed in streaks and interrupted bands extending from the disorganized and disrupted cells of the stratum germinativum right through the dermis, often enclosed in a cylinder of round cells. This focalization resembled somewhat the localization of the

granuloma in tuberculoid leprosy. At the level of Unna's palisade layer, the melanin might be distributed in a line parallel to the surface of the skin. In other cases, the masses of melanin were all of similar size, and rounded, giving the impression of being enclosed within a limiting membrane.

The dispersal of particulate masses of melanin deep in the dermis would, in conjunction with the brown colour of the normally pigmented skin, give rise to the various shades of blue-grey and blackish-brown coloration observed clinically.

DISCUSSION

Unlike the reported findings in animals receiving isoniazid in addition to B 663 (Chang 1962), the appearance of the ruddiness and hyperpigmentation was not postponed in those patients taking another drug (dapsone, or dapsone and ditophal) in addition to B 663, nor was the apparent intensity of the red or the black pigmentation modified.

The widespread staining of the tissues by the safranins and the presence of microcrystals of B 663 in macrophages as well as extracellularly, do not appear to induce any cellular response in the experimental animal beyond a slight foreign body reaction. No local or systemic toxic effects at comparable dosages have been observed, nor has any carcinogenic effect been seen on prolonged administration of the drug. With long-continued high doses, however, the drug accumulates in the liver, and the possibility of toxic manifestations must not be overlooked (Shepard 1964; Chang 1964).

That the hyperpigmentation may have a complex pathology, is suggested by the work of Knight (1964) and Wertlake (1964), who investigated two Mexican patients under treatment with B 663 at the National Institute of Allergy and Infectious Diseases, Washington. These workers were unable to detect significant differences in the amount of melanin pigment present in sections of skin taken from various sites, and suggest that a variable pattern may exist.

The hyperpigmentation is similar in some respects to that reported by Lowe (1952) in breast-fed babies whose mothers were taking dapsone. Doull (1959) noticed a hyperpigmentation virtually confined to areas of lepromatous infiltration in patients taking high doses of amodiaquin for long periods (Browne 1961). Some patients develop a generalized hypermelanosis following treatment with dapsone (Browne 1959, 1964), but in very few is the hyperpigmentation limited to skin affected by discrete or diffuse lepromatous infiltration. The hyperpigmentation observed in these patients under treatment with B 663 is unlike both the diffuse fixed eruption resulting from hypersensitivity and a generalized post-inflammatory hypermelanosis.

In spite of the changes in skin colour which might be objectionable in the lighter-hued, it is reassuring to observe that both the ruddiness and the hyperpigmentation diminish after the cessation of treatment and eventually disappear completely.

SUMMARY

The clinical and histological features of the red and black pigmentation of the skin developing in the course of treatment of leprosy patients with B 663 are reviewed. The coloration *per se*, being transitory, should not constitute an insuperable cosmetic objection to the use of the drug, especially in patients living among a population showing some considerable range of skin pigmentation.

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A Limited Clinical Trial of Injectable Thiambutosine

(Ciba 1906)

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The inconvenience and expense of giving thiambutosine orally two or three times a day, coupled with the fact that a variably high proportion of the drug is not absorbed from the digestive tract, have stimulated the search for a method by which the drug can be given at less frequent intervals, at a lower dosage and with a higher utilization ratio.

To this end, Messrs Ciba Limited, of Basle, the makers of thiambutosine, a proprietary diphenyl-thiourea (Ciba 1906, or 'DPT'), have prepared a 20 per cent suspension of their product in arachis oil. Experimental studies in the mouse have shown that this concentration of the drug in this vehicle is well tolerated locally and systemically. The active product is gradually released over a period of two to three weeks.

Patients

For this small pilot study, four untreated patients were selected – two had lepromatous leprosy, and two bacteriologically positive borderline leprosy. Their weights ranged from 100 to 127 lbs.

Dosage

For 18 months, fortnightly injections of 10 ml. of the 20 per cent oily suspension were given into the quadriceps extensor femoris, a different site being used on each occasion. Careful injection technique included cleaning the site with an alcohol-impregnated swab; a slow, steady injection; complete injection of the product before withdrawal of the needle; prolonged and gentle massage of the site.

At this point, the injections were discontinued and dapsone was substituted, beginning with 100 mgm. twice weekly for three weeks, increasing to 200 mgm. twice weekly for three weeks, and thereafter 300 mgm. twice weekly.

Local tolerance

Local tolerance was perfect. The injections were virtually painless. Some patients complained of very slight and transient 'heaviness' at the injection site. No infection or abscess was seen, and no oozing of the injected material from the needle-puncture.

General tolerance

No systemic toxic symptoms were reported.

Results

Results were comparable with those of thiambutosine administered orally.

Clinical improvement

Clinical improvement was noted in all patients, being most marked in the two with borderline leprosy. This improvement was continuous. The patient showing least improvement was an old man with advanced nodular lepromatous disease.

Bacteriological improvement

The bacteriological improvement ran *pari passu* with the clinical progress. Normal-staining solid rods of *M. leprae*, which had been present in the following approximate percentages in the four patients: 60, 60, 100, 80, disappeared finally from all eight sites smeared after the lapse of 15, nine, five and three months respectively. The reduction in the Bacterial Index was 81 per cent at the end of the 18 months of thiambutosine therapy.

Substitution of dapsone for injectable thiambutosine was accomplished without incident, and progress thereafter was maintained at approximately the same rates as before.

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'Resistance'

In spite of the progressive reduction in the Bacterial Index, normal-staining solid rods began to reappear in the nasal mucosa of the one patient referred to above, two months before the cessation of thiambutosine treatment, *i.e.* during the 16th month. These persisted and became proportionately more numerous, eventually attaining an average of 22 per cent of the total number of recognizable bacilli present in the smears from the nasal mucosa. Smears of the ear-lobes and then of some skin sites showed normal forms, which, however, never exceeded 10 per cent of the total. Then, during the 18th and 19th months, the Bacterial Index rose from 0.9 to 2.5 and remained above 0.9 for 10 months. By the end of 30 months of treatment (*i.e.* 18months of injectable thiambutosine followed by 12 months of dapsone), the Bacterial Index and the Morphological Index (= the percentage of solid-staining rods) had both returned to the level existing at the 16th month.

Reaction

Neither of the two lepromatous patients experienced erythema nodosum leprosum, and no patient developed peripheral neuritis while under treatment with injectable thiambutosine or while subsequently taking dapsone orally.

Conclusions

The therapeutic effect of injectable thiambutosine appears to be comparable with the orally administered product. In this small series, local tolerance was excellent, but the possibility must be taken into account of separation of the drug from its vehicle and its concentration at the periphery of the injected suspension. There are certain practical difficulties inherent in the injection of a viscid liquid in doses of the order of 10 ml. fortnightly, which must be recognized when contemplating mass treatment.

There is a restricted area of usefulness for a well-tolerated injectable alternative to dapsone.

The development of 'resistance' during the second year of administration of injected thiambutosine recalls its occurrence after oral administration of the product.

SUMMARY

Ten ml. of a 20 per cent suspension of thiambutosine (Ciba 1906) in arachis oil was given intramuscularly at fortnightly intervals for 18 months to a group of four patients. The injections were well tolerated. The clinical and bacteriological improvement noted was on a par with that in similar patients taking the drug orally.

ACKNOWLEDGEMENTS

I wish to express my thanks to Messrs Ciba Limited, for supplies of injectable thiambutosine (Ciba 1906), and for providing experimental evidence and references, and to Dr S. O. Egwuatu, Chief Medical Officer, Ministry of Health, Eastern Nigeria, for permission to publish this article.

'Isoxyl' in the Treatment of Leprosy A preliminary Report

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Buu-Hoi (1954) reported good results with this drug in three patients who had tuberculoid leprosy which was resistant to 'Disulone' and chaulmoogra oil. He later reported on a daily dosage of 400 mgm. in lepromatous patients (Buu-Hoi 1961).

'Isoxyl' is 4-4¹ di-iso-amyloxythiocarbanilide, and was tried by him because it is a potent antituberculous chemotherapeutic agent, as shown by Mayer *et alia*. in 1953, and it is chemically related to the useful N¹N¹-diphenylthioureas, of which thiambutosine ('Ciba 1906') is a foremost example in leprosy.

Buu-Hoi and his colleagues in Vietnam had been using 4¹4¹diethoxycarbanilides (as 'Dialide' or 'Etoxid') with success in leprosy. Then the 4 4¹ di-isoamyloxy substituted carbanilide, more potently tuberculostatic, became available at a reasonable price from Continental Pharma as 'Isoxyl'.

Dr J. Ross Innes, Medical Secretary of the British Leprosy Relief Association, London, told me about this compound, and the makers (Continental Pharma) generously supplied me with enough 'Isoxyl' for a small clinical trial in patients at Liteta Leprosarium.

Twelve patients who had lepromatous or near-lepromatous leprosy, and who had had no previous treatment, were included in this trial. Results to date seem sufficiently encouraging to justify an immediate preliminary report, but I am well aware that a longer period of study is needed in order to assess the exact status of the drug.

Observations so far indicate remarkably rapid clinical improvement, with regression of lepromatous nodules in three to four months. The drug is very acceptable to the patients, and erythema nodosum leprosum ('E.N.L.') and other acute exacerbations have been infrequent. The toxicity of 'Isoxyl' is very low.

METHODS

All 12 patients were Africans. They had routine physical examination, and suitable colour photographs were taken. On admission, and threemonthly thereafter, skin biopsies were taken; on the subsequent occasions the biopsies were taken either close to the original biopsy site, or from a comparable lesion-site (as in the method of Ridley and Jopling 1962). At the time of each subsequent biopsy, further clinical photographs were taken. The biopsies were submitted to Dr R. G. Cochrane, Director of the Leprosy Research Unit, London, and I am most grateful to him and to his colleague, Dr D. J. Harman, for their invaluable aid.

Skin smears were taken by the 'scraped incision' method of Wade and Rodrigues (1927), stained by Ziehl-Neelsen's method, and reported on by an experienced laboratory technician. Ridley's modification (1958) of Cochrane's scale was used to record the bacillary index, and the proportion of solid bacillary forms was also recorded.

Routine ancillary examinations carried out were: photo-colorimetric estimation of haemoglobin, examination of blood for sickling, Erythrocyte Sedimentation Rate ('E.S.R.'), and examination of urine and stool specimens.

Although I usually employ the classification of Cochrane and Smyly (1964) for clinical purposes, in this trial group the research classification of Ridley and Jopling (1962) has been used.

All patients admitted to Liteta Leprosarium have their chest X-Rayed on admission, and this examination is repeated annually, or more frequently for special indications.

Once every three months the patients were re-examined, and they were also seen at any time if new symptoms developed, especially if possibly caused by exacerbations ('reactions').



Patient 6, "AK". 1. Transparency 1: 8th May 1964. Patient's face: to show thickened skin, especially on cheeks.



2. Transparency 2: 16th November 1964. Face: to show considerable improvement; some thickening of skin of nose and left cheek still obvious.



3. Transparency 3: 8th May 1964. Back: to show multiple small nodules.



4. Transparency 4: 16th November 1964. Back: to show complete resolution of nodules, which are now replaced by small, flat, black macules.



Patient 8, "Z.A." 1. Transparency 5: 8th May 1964 Face: to show extremely numerous small discrete nodules on face.



2. Transparency 6: 16th November 1964. Face: to show considerable flattening of the nodules; there are, in face, now no discrete nodules, but there is still a good deal of thickening of the skin of the forehead, nose and checks. The patients in this group were all well enough to lead an active life without being admitted to the hospital wards at Liteta.

The 'Isoxyl' was given orally as tablets, each containing 100 mgm. Dosage was 100 mgm daily, increasing weekly by increments of 100 mgm. daily to 400 mgm. daily, in ten of the patients. Two patients were given 400 mgm. daily from the commencement of their treatment. (This dosage is very small in comparison with that used in the treatment of tuberculosis, when up to 8 grams daily are given (Mitchell 1963).)

A lepromin test was carried out on all the patients; the lepromin was supplied by Chaussinand and Bourcart of the Pasteur Institute, Paris, and I wish to extend to them my thanks for this help.

RESULTS

Detailed clinical records are available for each patient; in the following table only a summary of findings is given: ment; this patient had one mild bout of erythema nodosum leprosum ('E.N.L.'). No other acute exacerbations ('reactions') occurred in any of the other seven patients. The 'Isoxyl' was not discontinued during the bout of 'E.N.L.'. The only possible toxic effect was the occurrence of a mild anaemia in one patient.

SUMMARY

1. Eight patients suffering from leprosy, all smear-positive, have been treated with 'Isoxyl' for periods of six months (seven patients), and ten months (one patient). None had had any previous treatment.

2. Seven had lepromatous, and one near-lepromatous, disease.

3. All have shown very good or excellent clinical improvement.

4. Bacteriologically, two showed much improvement, four showed some improvement, and two have shown no improvement as yet.

5. There was only one mild exacerbation ('reaction') in one patient.

Patient	Clinical Type or Group	Duration of Treatment	Exacerbations	Toxic Effecis	Bacteriological Progress	Clinical Progress
 Y.K. A.L. G.C. M.M. K.P. A.K. G.S. Z.A. 	L.L. B.L.* L.L. B.L.* B.L. L.L. L.L. L.L	9 months 6 months 6 months 6 months 6 months 6 months 6 months 6 months	Nil Nil Nil E.N.L. (mild) Nil Nil Nil	Nil Nil Mild anaemia Nil Nil Nil Nil Nil	Improved Improved Little change Greatly improved Much improved Improved Improved No change	Excellent Very good Excellent Excellent Very good Excellent Excellent Very good
9. L.N. 10. J.B.B. 11. L.M. 12. K.S.	L.L. B.L. B.B. L.L.	5 months 2 months 2 months 2 months	E.N.L. (mild) Mild neuritis Mild neuritis Nil	Nil Nil Nil Nil	Little change Much improved No change Improved	No change Too early to assess Too early to assess Too early to assess

TABLE Summary of Findings

*Patients 2 (A.L.) and 4 (M.M.), although clinically 'B.L.' were lepromatous histo-pathologically in skin biopsies: 'L.L.'.

Seven patients with lepromatous leprosy, treated for six months with 'Isoxyl', have shown very good or excellent clinical progress, and five have shown bacteriological improvement. One patient with borderline ('dimorphous') leprosy has shown, after six months treatment, very good clinical and bacteriological improve-

6. A mild anaemia developed in one patient.

CONCLUSIONS

This trial has so far proceeded for far tooshort a period for firm conclusions to be drawn, but it can be said that, so far, the results of Buu-Hoi *et alia*. (1961) have been confirmed, and the drug is so far very encouraging in its clinical effectiveness, patient toleration, and lack of toxic effects.

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The Surgical Management of Foot Deformities in Leprosy

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Trophic ulcers (or 'plantar ulcers') may occur on structurally normal but anaesthetic feet, and these have been called the 'dynamic type' ulcer, by Price (1963). They occur on pliant feet, heal rapidly with rest, and can be prevented by appropriate shoes. On the other hand, the presence of a deformity may promote recurrent and intractable ulcers even when shoes are worn. Ulcers associated with a fixed deformity have been called by Price the 'static type'.

Untreated, these feet ultimately undergo total destruction, and may be considered for amputation. Lately, however, it has become clear that many of these feet can be salvaged and made useful again by corrective surgery and appropriate shoes. The classification of foot mutilations resulting from leprosy has been the subject of a separate communication (Lennox). Five groups of deformity were described, and their main features discussed. It is the purpose of this paper to review those surgical methods which in the author's experience are useful in managing deformities which have a specific relationship to ulcers.

THE SURGICAL TREATMENT OF GROUP I DEFORMITIES

Dropped foot

In a study of plantar pressures during walking using pressure sensitive transducer discs, it was shown that in the dropped foot there was an accentuation of pressure along the antero-lateral border of the foot (Bauman *et al.*). It is here that the characteristic ulcers of the deformity occur. It should be one of the objects of surgical treatment to eliminate this pressure accentuation, and hence to remove an undoubted predisposing factor. A simple method of detecting this pressure in dropped foot is to take foot-print using an inked rubber mat (technique described by Price, 1963), on which accentuated pressures show as areas of heavy inking. A similar impression taken after operation will show the extent of pressure reduction obtained. Most examples of foot drop are complete, but in some instances, sparing of the peronei is seen. With strong peronei and absent tibialis anterior, the lateral balance of the foot is upset in favour of the evertors, and pressures along the antero-medial border of the foot are accentuated, causing a tendency for ulcers to occur here. Typically, absorption of the medial ray of the foot then occurs. The pattern of absorption of a damaged foot and the location of ulcer scars has an important bearing on the choice of foot drop correction.

Equinus deformities are easily corrected by a tendon transfer, and the operation of choice is transplantation of the tibialis posterior tendon into the dorsum of the foot. One of the principles of reconstructive surgery is that no tendon transfer should be carried out until the pattern of paralysis has become stable. Thus, timing of the transfer is of importance. It is not always easy to be satisfied on this point in cases of lateral popliteal paralysis. Lateral popliteal paralysis can recover and in cases of sudden or rapid onset (usually borderline cases), the prognosis may be comparatively favourable if the knee is promptly immobilized in a full length leg plaster. However, experience shows that recovery is unlikely to occur if six or more months have elapsed since the onset of the paralysis so that it is our custom not to operate before this time, but to operate as soon after six months as possible. Very occasionally, a spontaneous recovery of the anterior tibial muscle has been seen after tibialis posterior transfer, but this causes no untoward effect providing the plantar flexors are intact.

The presence of active peronei may be regarded as evidence that a stable pattern of paralysis has not been reached. This may be true, but a period of observation will show



FIG I A foot remnant rendered stable by Pantalar Arthrodesis, and the final appearance wearing a boot.



FIG 2 A fixed Equino-varus foot, showing the scarred area on the lateral border, and the soft tissue contracture behind and medial to the ankle. This foot requires Tibio-calcaneal fusion.





FIG 3 An Equino-varus foot remnant rendered stable by Tibio-calcaneal fusion, and the final appearance in a sock and sandal.



FIG 4 A Neuropathic right foot rendered stable by Triple arthrodesis.

whether recovery is occurring, or whether the paralysis is progressing. If there is evidence of recovery, then conservative management is indicated (a toe raising spring harness); if the peronei are weakening, then surgery should be undertaken as if the case were one of complete foot drop. In patients receiving regular medication, if the strength of the peronei appears to be constant, surgery is undertaken, but a different type of correction is selected. It is undesirable to defer foot drop surgery for too long pending a decision on the course being followed by the peronei. Patients dislike wearing foot lifting harness for longer than necessary, and a delay in surgery delays their ultimate rehabilitation.

How soon after the healing of an ulcer on a dropped foot should one carry out a surgical correction? There is no hard or fast rule, but it is our custom to wait for four weeks, and this system has worked well in practice.

The operation of tibialis posterior transfer as applied to leprosy patients has been well described (Gunn and Molesworth 1957), (Selvapandian and Brand 1959), and it is not necessary to repeat the descriptions. It is now our custom to employ a modification of the interosseous route, and to attach the transfer to the lateral cuneiform without disturbing the bone. This is to ensure a good lift to the lateral border of the foot, and this, combined with removal of the tibialis posterior from its rôle of invertor, eliminates the accentuated lateral pressures. Lateral balance is usually good. If later a valgus deformity develops, it is treated by a subtalar fusion of Grice-Green (1952) type.

In the presence of strong stable peronei, either a circumtibial tibialis posterior transfer or an interosseous transfer with a more medial insertion is required, so that lateral balance of the foot may be achieved. If the peronei later becomes paralysed, it may become necessary to shift the insertion of the transfer laterally, to tenodese the peroneus brevis to the transfer, or to perform an arthrodesis. Because, one can never be sure in leprosy whether apparently strong peronei will later become paralysed or not; these muscles are not used as prime dorsiflexors.

A successful foot drop correction will restore active dorsiflexion to the foot, restore the gait to normal, give a laterally balanced foot, and a normal distribution of plantar pressures. As these feet remain anaesthetic, they also require a simple shoe. Shoes alone do not afford protection against ulcers on a dropped foot.

Claw Toes

A number of operations have been described for this deformity, and before the toes become stiff correction by multiple transfer of the flexor digitorum longus tendons into the extensors is a simple procedure, and gives good results. Taylor (1951) reviews the operation and its good results in 68 (non-leprosy) cases. The results in leprosy are equally gratifying. The objects of the operation are (a) to correct the alignment of the toes so that the pulps came into contact with the ground; (b) to replace the fibrofatty pad beneath the metatarsal heads. This may be difficult once ulceration has occurred and the scars tether the skin to the underlying bone. There is no doubt that the time for correction is before ulcers have occurred. This simple operation is not used often enough in the early stages when the deformity is easily corrected.

Once the metacarpophalangeal joint begins to subluxate and the deformity begins to pass into group II, the difficulties of a successful correction are increased. Manual toe stretching by a physiotherapist is a useful but much neglected way of correcting a mild subluxation, after which a tendon transfer will suffice. A preliminary subcutaneous extensor tenotomy may help; but in many cases a dorsal capsulotomy and extensor lengthening are needed at the time of correction. Longstanding cases usually have a skin contracture as well so that a skin graft may have to be employed to cover a defect created over the dorsum of the forefoot. If it appears likely that a claw toe correction will involve a skin graft, extensor tenotomy, metacarpophalangeal capsulotomy, and tendon transfers or proximal interphalangeal arthrodesis, then amputation of the clawed toes is a better procedure (Nissen). This may, in any case, be the only choice for rigidly clawed toes perched dorsally upon the metatarsal necks, and subject to frequent shoe blisters. This operation has been employed for the ischaemic clawed toes in diabetes (Oakley et al) in Rheumatoid Arthritis, Hallux Valgus and Pes Cavus (Flint and Sweetnam). In many of these conditions, pain is the crippling symptom. This prevents the patients from walking and thus from getting ulcers or blisters. In leprosy, there is no pain but the rationale of operation is similar. By removing the subluxated toe, the displaced fibro-fatty pad is allowed to drop back under the metatarsal head. This will only happen if there are no scars between the skin and the underlying bone. This operation therefore is for the relatively unscarred forefoot. In sensitive foot, the operation causes no disability though patients find it easier to

balance in a normal shoe with a filled in toe. In the pressure disc study (Bauman *et al*) it was found that the feet shortened by trophic ulceration (and therefore, scarred) loss of toe function resulted in accentuation of anterior pressures. But, if the anterior pad drops back into place under the metatarsal heads, then sufficient tissue reserve becomes available to withstand the stresses of ordinary activity. Nevertheless, in leprosy cases, a moulded arch insole or a metatarsal bar shoe should be given in order to spare the metatarsal heads as much as possible from the extra pressure occasioned by loss of the toes.

When there is scarring under the metatarsal heads, the following operation, which is useful in Rheumatoid Arthritis deformity, may be considered. Through an anterior incision just in front of the weight bearing surface, all the metatarsal heads are excised. In leprosy feet, this is useful where there are multiple ulcer scars under the distal metatarsal arch and where the metatarsal heads are particularly prominent. Patients agree to this operation more readily than to total amputation and the results are functionally satisfactory, apart from the hazard of friction from shoes against anaesthetic toes.

An amputation through the metatarsals (Lisfranc) combines the advantages of removal of anaesthetic deformed toes with excision of bony points, and is required for cases with extensive anterior plantar scarring. A level of bone section can be selected which allows easy closure with dorsal and plantar flaps, and a substantial pad of plantar pulp can be arranged to underly the front of the bony skeleton. Unfortunately we have not been able to employ this excellent operation as often as we have advised it, due to willingness of many of our patients to sacrifice their toes, whatever the risk of ulcers.

THE SURGICAL TREATMENT OF GROUP II DEFORMITIES

The important features of this group of deformities have already been described. In addition to reduction and deflection of plantar surface, marginal scarring and concentration of weight bearing onto small areas, it has been shown that in the shortened foot, anterior pressures at 'push off' are significantly higher than those in feet of normal length (Bauman *et al*). The aims of treatment may be stated thus:

- (a) To restore all the available plantar surface to its weight bearing function;
- (b) to relieve scarred areas from weight bearing and shearing stresses;
- (c) to correct and stabilize the deformity by bone surgery or tendon transfer;
- (d) to modify excessive anterior push off pressures and protect the foot by suitable shoes.

These principles may be applied to the deformities of this group as follows:

The shortened equinus foot

This foot ulcerates anteriorly. The deformity is fixed by shortening of the tendo achilles, and contracture of the ankle capsule. The tibialis posterior is usually present and active. Correction can be obtained by a single or two-stage soft tissue operation, viz., lengthening of tendoachilles, posterior capsulotomy and tibialis posterior transfer. The management is then that of a tibialis posterior transfer. It is not common to obtain a large range of movement after this operation but this does not matter as long as the foot is maintained at about 90°.

Difficulty is sometimes encountered due to the extreme shortening of the structures behind the ankle joint, notably the skin, which in this type of case is usually contracted and lacking in resilience. The procedure to be adopted depends on whether there is hope of movement at the ankle joint or not (examination of an X-ray is helpful). If it is felt that movement can be expected, then all the posterior structures should be drastically lengthened, and the foot brought up at least to a right angle. In order to achieve this, a large flap of calf skin may have to be mobilised in continuity with the heel, and induced to slide downwards as the foot is dorsiflexed. The defect over the upper calf is then grafted with split thickness skin. At a second stage the tibialis posterior is transferred onto the dorsum of the foot to provide active dorsiflexion.

This procedure is not justified if there is no hope of ankle function afterwards. It is then better to carry out a pantalar arthrodesis (Fig. 1). Even this may not be feasible when extreme posterior soft tissue contracture does not allow the foot to be brought up to a right angle. In these circumstances we excise the talus, and fuse the lower end of the tibia to the calcaneum.

The shortened plantigrade foot

This requires special shoes to modify the high anterior pressures at 'push off'. On the basis of the pressure disc study (Bauman *et al*) rigid sole rocker shoes were recommended. Unfortunately these have proved to be unsatisfactory in practice, and we now emply modified metatarsal bar shoes or ankle boots.

The inverted foot and the shortened inverted foot

Simple inversion is corrected by means of a subtalar arthrodesis with excision of a laterally based wedge. It is important to aim at over correction rather than exact correction, as the position of the finished foot is often not as good as appeared on the operating table.

In many cases there is an associated foot drop with an active tibialis posterior. The choice of operation again depends upon whether a mobile ankle joint is expected or not. If surgery is undertaken with hope of a functioning ankle, then a two-stage correction is undertaken, as follows:

- (i) Triple arthrodesis with resection of an appropriate wedge for correction of the inversion.
- (ii) Lengthening of the tendo-Achilles, posterior capsulotomy of ankle, and tibialis posterior transfer.

If there are degenerative changes in the ankle joint, or other reasons for supposing that active dorsiflexion may not be achieved then a pantalar arthrodesis is carried out, and the anterior lever of the foot is shortened.

The fixed, inverted, equinus foot is often more difficult to correct than might be expected. The reason for this is that the soft tissues on the concave side of the deformity have contracted and become fibrosed, and not infrequently joint surfaces are the seat of fibrous ankylosis (Fig. 2). After excision of a wedge based upon the convex side of the deformity, the contracted soft tissues on the medial side may be tough enough to prevent closure of the wedge, even when the apex of the wedge is of significant thickness and extends cleanly through to the medial side of the bone. Experiences of this kind with the severe fixed deformity have led us to advise excision of the talus and tibio-calcaneal fusion as the operation of choice. Some length is sacrificed, but the contracted tissues are relaxed sufficiently to permit alignment of the foot on the tibia at 90° and without inversion or eversion (Fig. 3).

THE SURGICAL TREATMENT OF GROUP III DEFORMITIES

These are deformities due to neuropathic destruction of bones and joints. The mechanism of initiation of breakdown of these feet is not clearly worked out. An extensive study of paralytic feet resulting from poliomyelitis enabled Grice to state that loss of support to the head of the talus appeared to be the cardinal cause of breakdown of the arch in these feet, and that breakdown of the support was initiated by the valgus posture consequent upon weight bearing on the unsupported foot. In valgus, the talus slides forwards and medially relative to the calcaneum so that the head loses most of its bony support, and relies more on the calcaneonavicular ligament. This movement of the talus is accentuated by (i) the upward and backward pull of strong calf muscles on the calcaneum: (ii) the forward and downward thrust imparted to the talus by body weight; (iii) loss of tibialis posterior and tibialis anterior (in polio). In leprosy, tibialis posterior is spared, but support of the talo-navicular region is reduced by paralysis of the tibialis anterior, so that additional strains fall on the spring ligament. Normally, the plantar ligaments are strong enough to withstand the static strains placed upon them (Basajian and Stecko), but if the ligaments are softened or slackened from any cause, and the plantar and extrinsic foot muscles are paralysed then the ligaments may be expected to stretch. When this happens, the talar head drops, the lines of thrust and the mechanics of the midtarsal and other joints will be altered, and without the protection of pain, joint damage and neuropathy may be expected to set in. Factors which would soften or damage plantar ligaments may be listed as follows:

- (1) Septic arthritis or osteomyelitis anywhere in the foot.
- (2) Trophic ulceration anywhere in the foot.
- (3) Painless fractures of the foot bones (relatively common occurrences in the anaesthetic foot).

All these conditions cause hyperaemia and oedema of the foot and therefore probably softening of the plantar ligaments. Being insensible of pain, the patient continues to walk, or is allowed to by his doctor. Then the ordinary stresses of walking, quite safe for normal ligaments, are likely to cause stretching of the odematous ligaments, and conditions are set for a neuropathy. The above conditions frequently occur in the leprosy foot, though this account can at present be little more than a working hypothesis. Nevertheless, it does raise the question of whether an extended period off weight bearing during acute ulceration, followed by a period of protected weight bearing, might not prevent the later development of neuropathy in leprosy feet. It is true that trophic ulcers in general heal while in a plaster cast, but it may be the patients who are most active in their plasters who later develop neuropathy.

Once neuropathy is established, arthrodesis is the operation of choice. It stabilises the foot and arrests an otherwise progressive condition (Fig. 4). Inlay grafts of cancellous bone have also been successful. Once it is certain that neuropathic degeneration has set in, operation should not be delayed. Surgery is easier and fusion more certain before bones become destroyed and sclerosed, and relationships distorted.

THE SURGICAL TREATMENT OF GROUP IV DEFORMITIES

Spurs on the undersurface of the calcaneum are frequently associated with an active ulcer or a scar, and sometimes with a smouldering osteomyelitis of the undersurface of the calcaneum. There may be associated sinuses. All these conditions are conveniently dealt with by an operation through a fishmouth incision round the heel margin. A flap is developed which reflects skin, heel pulp, plantar fascia and periosteum distally. The undersurface of the calcaneum is then trimmed flat with a sharp osteotome, cutting away all excresences and depressions. The flap is then allowed to fall back into place and the incision is sutured. Sloughing of the flap is an occasional complication. The risk of this is much reduced by carrying the incision along the lateral margin of the heel only, thus sparing the medial calcaneal vessels. Heel sinuses often connect with a focus of osteomyelitis on the undersurface of the calcaneum, and in these cases, the incision should be drained, and the sinus tracts either excised or curetted. A small scar in the flap can often be excised by an elliptical incision followed by primary suture if there is sufficient tissue laxity to allow closure without tension. On occasion small clean

ulcers have been treated by this method without mishap.

THE BIZARRE HEEL DEFORMITY

This results from loss of calcaneum or talus, or parts of both, from osteomyelitis or neuropathy. With weight bearing, these deformities are unstable and progressive. It is not possible to apply a standardized operation to each variation but the principle of treatment is simple. Stabilization of the bony remains by whatever technique seems best suited to the particular case. The bones in these cases may often exhibit sclerosis, and the operator encounters tough interosseous fibrous tissue. As much as possible of this undesirable tissue should be removed. Fusion is most likely to occur with a compression technique, reinforced by cancellous bone shavings, or by a cancellous inlay or strut graft.

These operations never give a foot of glamorous appearance, but they usually result in a foot, which, with a carefully made shoe, and some care, can be walked on.

THE SURGICAL TREATMENT OF GROUP V DEFORMITIES

Calcaneus deformity is uncommon, and treatment to some extent depends upon the cause. If it results from excessive tensioning of a tibialis posterior transfer and there is sufficient passive plantar flexion at the ankle, it may be treated by lengthening the dorsiflexor and shortening the tendo-achilles. Some anterior skin contracture may be encountered and may necessitate a skin graft. All other cases require pantalar arthrodesis.

GENERAL MANAGEMENT OF FOOT RECONSTRUCTION CASES

Many of these patients are anaemic and debilitated by long ulceration, sepsis, and malnutrition consequent upon inability to earn. Deformed feet are often fissured and orthopaedically very dirty. The legs may be covered with scabies and eczema. The case may present with open ulcers. It is the custom to admit these cases and to heal the ulcers by rest, elevation and Eusol dressings. In the meantime anaemia is corrected by oral or parenteral iron supplements, and the skin is brought into the best possible condition by scrubs and oil applications. Severe degrees of anaemia are transfused. A daily leg exercise class has helped to stimulate circulation and when the ulcers have healed, selected cases are given exercises on a bicycle ergometer, again with the object of developing the circulation. About six weeks after the last ulcer has healed, surgery of the underlying deformity is undertaken. In the case of foot drop, however, where the procedure is confined to the dorsum of the foot, surgery is undertaken after four weeks. These are arbitrary time periods with no special merit other than that they allow latent infection to either die away or manifest itself. They do not unduly delay the ultimate rehabilitation of the patient, and they have worked well in practice.

Where bony fusion is concerned, the most reliable results have been seen after employment of a compression technique, though an occasional troublesome pin track infection is seen. Our experience has been that plaster of Paris fixation alone, or internal fixation with Kirshner wires, does not promote sound bony union with predictable regularity. Staples have also been tried. They are convenient to use but are less likely to promote union unless the areas of cancellous bone in contact are large. The greater the degree of sclerosis present, the less the chance of sound bony union and we are using grafts of iliac cancellous bone more and more frequently. Post operatively, the leg is kept elevated in its padded cast. Next day straight leg raising and knee flexion exercises are commenced. After four weeks, the sutures are removed, after which X-rays are taken and the 'feel' of the arthrodesis is tested. In favourable cases, the compression pins may be removed, and a new padded plaster is applied. Weight bearing is allowed after six to eight weeks.

The arthrodesis will consolidate in 12 to 16 weeks, after which the foot is ready for shoe fitting.

DISCUSSION

None of these operations will succeed unless a shoe is also worn, and surgery on the more mutilated feet has only become possible with the development of simple techniques for making moulded insoles. In many instances, the result is an unglamorous walking appendage, which, nevertheless, gives good functional service if properly cared for. This raises the question of selection of patients for salvage procedures. Only patients who have insight into their condition and into what is being attempted for them are likely to be benefited from these often intricate procedures.

The surgeon who sets out to salvage badly damaged feet must accept that he is operating on risky material, and must be prepared to lose an occasional foot. It is wise to explain this to the patient beforehand. Many of these feet would, in any case, be properly considered for amputation, so there is little to lose in attempting salvage if the patient is told at the beginning not to hope for too much. The difficulties of limb fitting to an anaesthetic stump are by no means as small as some writers suggest, so that a salvage procedure made possible by the assistance of the shoemaker, is by no means an unattractive alternative.

Hodges (1956) reported the use of a triple arthrodesis of Lambrinudi type on 15 cases of leprosy foot drop with acceptable results in all cases. We have had no experience of the use of this procedure, since all our cases have been treated by the simpler methods described. However, the method appears to be useful in cases of severe equinus where complete correction cannot be achieved by other forms of arthrodesis.

SUMMARY

The management of Leprosy foot deformities which are closely associated with trophic ulcers, is described. Emphasis is placed upon reconstructive and salvage procedures rather than upon amputation.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the constant encouragement and guidance of Dr A. J. Selvapandian; also the help of Mr S. D. Sigamoney in the preparation of the photographs; and Mr B. V. Venkatesan's careful typing of the manuscript. This work has been made possible by funds made available by the Vocational Rehabilitation Administration, Washington, USA, and the British Leprosy Relief Association.

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A Varicelliform Eruption appearing in the course of Acute Exacerbation of Lepromatous Leprosy

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The well-known skin lesions that occur during acute exacerbation in lepromatous leprosy assume many and diverse forms. One of the least common is a varicelliform eruption.

CASE REPORT

The patient was an Ibibio male of about 35 years of age. He was admitted to the Uzuakoli Leprosy Settlement on 22nd February, 1964, suffering from lepromatous leprosy of probably three years' duration.

Clinical examination

The skin of the entire body except for the scalp, the axillae, the inguinal regions and the sacrococcygeal region was diffusely infiltrated and almost uniformly hypopigmented. He had not noticed the gradual loss of pigment or the thickening of the integument, but the sudden appearance of numerous lenticular nodules on his face (especially the forehead, cheeks, nose and chin), upper trunk and proximal parts of the limbs brought him for diagnosis and treatment.

Both the ulnar nerves were slightly enlarged just above the elbow, and tender. The other main superficial nerve trunks were normal.

Bacteriological examination

His Bacterial Index was high (4.0), innumerable bacilli and many globi being present in every field examined with the oil-immersion objective from every site smeared.

Mitsuda reaction

The Mitsuda reaction was completely negative.

Treatment

After the first dose of 0.025 g. dapsone, several

lesions of erythema nodosum leprosum – both acuminate and diffuse – made their appearance on the forearms, arms and thighs. The temperature rose to 100.8°F. (38.2°C.) The general symptoms were controlled by rest in bed and analgesics, and since no further local lesions occurred in the skin, dapsone was continued at the same dose, 0.025 g. twice weekly. With two months, the Bacterial Index (eight sites smeared) had fallen from 4.0 to 2.5 and the percentage of normal-staining bacilli from 87 to 13.

The varicelliform eruption

The dose of dapsone was then increased to 0.05 g. twice weekly. Within two days of receiving the first dose of 0.05 g., the patient complained of general malaise, accompanied by a slightly raised temperature. In many areas, the lepromatous infiltration of the skin of the face, trunk and limb became red and raised and papular. On the acuminate papules of many of the infiltrated masses, particularly on the chest and the scapular region, small vesicles numbering about a score suddenly made their appearance. These latter itched slightly. The individual elements were observed to maturate rapidly from the papular to the vesicular stage. Some of the vesicles burst spontaneously; others were scratched by the patient. Successive crops appeared during the following two weeks. No vesicles appeared on the lepromatous nodules themselves.

Microscopical examination of the opalescent fluid obtained from intact vesicles revealed scanty degenerate pus cells and very numerous *M. leprae*, arranged singly and normal-staining. No other organisms were found, in smears stained by either methylene blue or Gram's method.

Since there had been no cases of chickenpox

or of herpes zoster in the Settlement, these two conditions may be excluded.

All the varicelliform lesions eventually crusted over and scarred. The acute exacerbation subsided, and the patient resumed his interrupted clinical progress and his bacteriological improvement.

SUMMARY

A case is reported in which a varicelliform

eruption appeared on infiltrated skin lesions during acute exacerbation in lepromatous leprosy. The vesicles contained numerous M. *leprae*.

ACKNOWLEDGEMENTS

My thanks are due to Dr S. O. Egwuatu, Chief Medical Officer, Ministry of Health, Eastern Nigeria, for permission to publish this article.

An Improved Technique for the Histopathological Diagnosis and Classification of Leprosy

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The importance of biopsies in connection with the diagnosis, prognosis and treatment of leprosy is receiving greater attention among leprologists, and it is essential therefore that the fixation, processing and staining of tissue sections should be of a high standard if the finer points in relation to diagnosis and classification of leprosy are to be appreciated.

FIXATION

It has been accepted by many that 10 per cent neutral formol-saline is a poor fixative for most tissues, including human skin, because of its tendency to cause considerable shrinkage of the cellular structures, and this has proved to be a hazard in assessing the histopathological picture of leprosy correctly.

In many respects Zenker's solution is the most satisfactory fixative, but the need for running water or frequent changes of water when using this method renders it almost impracticable for those working under 'bush' conditions.

We have now found that the Zenker-formol variant recommended by Dr. D. S. Ridley, Consultant Pathologist at the Hospital for Tropical Diseases, London, meets the major conditions for good fixation of skin and nerve tissue to be examined, and the details of this method as used by us are as follows:

Formula

Solution A Formaldehyde 40 per cent 10 ml. Mercuric chloride 2 gm. Distilled water 90 ml. Solution B Glacial acetic acid.

The solution A is stable and a stock bottle of this must be kept available. The glacial acetic acid B is added to the solution A immediately before use, that is, at the time of biopsy. For the average biopsy 20 ml. of the fixative solution is adequate and is obtained by adding I ml. of solution B to 19 ml. of solution A. The tissue is

placed in this fixative for a minimum of 15 hours and a maximum of 24 hours. The fluid is then simply poured off and replaced by 70 per cent alcohol. After 24 hours the tissue is ready for processing, or may be despatched in the 70 per cent alcohol for processing elsewhere.

It is essential that the greatest care should be taken to prevent damage to the biopsy tissue. An excision with a sharp knife is preferable to a skin punch, and the tissue must not be crushed or pinched with forceps.

PROCESSING

The biopsy tissues are processed in the usual way by dehydration through alcohols, cleared in cedar oil, and impregnated and blocked with paraffin wax. Ribbon sections are cut at 5 microns, mounted and dried in an incubator at 37° Centigrade overnight.

STAINING

If the finer points of classification of leprosy are to be appreciated it is important that individual attention be given to the staining process, and we have found that a modified Masson's trichrome technique shows the details of the histopathology well and allows the physician to assess the stage of the leprosy process and to relate it to his clinical findings.

One of the drawbacks, however, has always been that the actual organism responsible for the disease, the *Mycobacterium leprae*, is not visible in the specimen stained by this Masson's stain, and that further sections have to be cut and stained by the Fite-Faraco modification of the Ziehl-Neelsen technique in order to see it. The changing over from one microscope slide to another is also time-consuming and in many instances inconvenient, so with this in mind it became desirable to adopt a technique for combining the above stains into one preparation, so

that the histopathologist would be able to see the whole picture of the presence of the bacilli in the tissues and their relationship to the resultant cellular response.

Not only does this increase accuracy in the diagnosis and assessment of the case, but it makes the histopathology of leprosy much more interesting and instructive, and the preparations are excellent for study and teaching purposes. Examination of only one slide is much more convenient, and there is economy in time and materials in the preparation of specimens, and in storage space. The histopathological picture obtained is also good for colour photography and we have found no difficulty in seeing bacilli or bacillary remnants even when only one or two are present in the section. In really doubtful cases a second section can always be stained by the Fite-Faraco technique to confirm the findings.

The routine use of this staining method for biopsies of granulomatous lesions of doubtful etiology would assist in the earlier dignosis of missed leprosy cases. This method is also equally suitable for the identification of *Mycobacterium tuberculosis* and its resultant pathology.

As this staining method is a combination of a trichrome stain and the Fite-Faraco stain, we have temporarily dubbed it the 'Triff' method, from 'tri' to indicate trichrome and 'ff' to indicate Fite-Faraco. The details of the method are as follows:

Triff Stain

(Mixture of Trichrome and Fite-Faraco stains)

- 1. Warm slide gently to melt wax.
- 2. Place in pure turpentine oil for one hour.
- 3. Blot gently with filter paper, wash in tap water, and place in common solution of iodine (0.5 per cent iodine crystals in 70 per cent alcohol) for five minutes to remove mercuric salts.
- 4. Rinse thoroughly with tap water.
- 5. Immerse in 1 per cent aqueous solution of sodium thiosulphate until bleached 10 to 20 seconds.
- 6. Wash in running water for five minutes.
- 7. Stain with cold strong filtered carbol fuchsin (Ziehl-Neelsen) for 30 minutes.
- 8. Wash off surplus stain with tap water for five minutes.
- 9. De-colourize with two washes of Fite de-

- colourizer (0.5 per cent hydrochloric acid in 70 per cent alcohol) rinsing with tap water in between each wash – approximately one minute each wash.
- 10. Wash thoroughly with tap water for 15 minutes.
- 11. Stain with Harris' haematoxylin for two minutes.
- 12. Wash in tap water until blue.
- 13. Rinse rapidly with Fite de-colourizer.
- 14. Wash for at least 10 minutes with tap water longer if possible.
- 15. Stain with 1 per cent aqueous yellow eosin for 30 seconds.
- 16. Wash thoroughly with tap water for 10 seconds followed by 70 per cent alcohol for 10 seconds.
- 17. Rinse over rapidly with absolute alcohol.
- 18. Stain with 2 per cent alcoholic solution of saffron* for 5 to 15 minutes. Control with the microscope to ensure differential staining of nerves and connective tissue a yellow colour rinsing in alcohol to remove excess saffron and replacing in the stain if not stained sufficiently.
- 19. Rinse rapidly with absolute alcohol.
- 20. Clear with xylene.
- 21. Mount under a coverslip in neutral Canada balsam or DePeX.
 - The staining scheme is:

Cell nuclei	blue
Cytoplasm	pink
Muscle	pink
Nerve tissue	yellow
Connective tissue	yellow
Acid-fast organisms	red

 $\mathcal{N}.B$. The use of a known positive control section is recommended with each batch of sections stained.

It is hoped that the publication of this method will give to histopathologists a new approach to the study of the pathology of leprosy, and that it will enable them to take a greater interest in the details of the cellular changes in leprosy in relation to the presence of the *Mycobacterium leprae* in the tissues. Careful use of this technique will, we hope, suggest avenues of research which it would be difficult to discern by the ordinary staining methods.

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^{*2} per cent alcoholic solution of saffron is supplied by G. T. Gurr Ltd., 136–144 New Kings Road, London, s.w.6.

SUMMARY

A technique for staining paraffin sections with a combination stain of a modified Masson's trichrome and the Fite-Faraco is described in detail, and the various advantages of using this method in the diagnosis and classification of leprosy are discussed.

ACKNOWLEDGEMENTS

We would express our appreciation to Dr. Ridley for the development of a satisfactory fixative for leprosy tissues. We would also like to express our thanks to Dr. R. G. Cochrane, Director of Leprosy Research Unit, London, for his encouragement and help in the preparation of this paper.

An Electrophoretic Study of Leprosy Serum and its possible relationship with Haemagglutination Titre

MRS GOURI BANERJEE* and A. N. ROY Indian Institute for Biochemistry and Experimental Medicine, Calcutta

Investigation on haemagglutination reaction of serum of leprosy patients have been made by various authors; and Gernez-Rienz *et al* (¹), Floch and Sohier (² and ³). Pissier and Sacret (⁴), Viet (⁵), Roy and Banerjee (⁶ and ⁷) got positive haemagglutination titre in sera of leprosy patients. Relationship between gammaglobulin content of serum protein and antibodies is now considered an interesting problem immunologically. Haemagglutination reaction is an antigen-antibody reaction, so a study of electrophoretic pattern of serum proteins and its possible relation with Haemagglutination titre of sera of leprosy cases was undertaken. The result of this study is presented in this paper.

MATERIALS AND METHODS

Separation of sera from clotted blood

Thirty-two cases of leprosy patients were examined. They were clinically diagnosed leprosy patients without any evidence of tuberculosis. Microscopic examination of smear made from skin lesions was also done. Ten normal adults selected from the workers of the Indian Institute for Biochemistry and Experimental Medicine were examined as controls. Ten ml. of blood was taken from the vein of each person in fasting state in the morning. Blood samples were kept in refrigerator at 4°C for serum to separate by coagulation and clear serum obtained by centrifugalization.

Paper-electro phoresis

The method of separation of different protein fractions of serum was that of Ganguli (⁸). Usually 20 cm Whatman filter paper No. I, was used, bromophenol blue and acetic acid solution were used for staining and washing respectively. The quantitative determination of the different fractions of serum was carried out according to Ganguli(⁹).

Preparation of sera for electrophoresis

One ml. serum of each case was taken in small test tubes and trace of bromophenol blue was added. The dye combined with the albumin and acted as an indicator for the length of the run given.

Haemagglutination reaction

The same method was followed as was done in our preliminary study $(^{6})$.

RESULTS

The distribution of different fractions of albumin and globulin from sera of normal and the leprosy cases is represented in Tables I and II.

	Total serum protein and distribution of its various fractions and haemagglutination titre in normal human subjects (Results of protein fraction in the average of 10 individual cases)								
Total Protein %	Albumin	a ₁	G a2	lobulin B	γ	– Total Globulin	A.G. Ratio	No. of Cases	Haemagglu- tination Titre
7.6	58.5	2.8	4.6	10.4	23.7	41.5	1.4	6 3	Negative 1 :2 negative

TABLE I

*Present address: Institute of Post-graduate Medical Education and Research, Calcutta 20.

DISCUSSION

In an earlier investigation Roy and Banerjee (7)demonstrated that there was no correlation between haemagglutination and tuberculin skin sensitivity reaction in leprosy. In the present study which was undertaken to see the possibility of a relationship between the serum protein fractions especially globulin fractions and the haemagglutination titre of sera of leprosy cases, it may be observed from Tables I and II that the albumin-globulin ratio between the normal and leprosy sera alters appreciably. Compared with normal sera (Table I) the globulin fractions of the leprosy sera got elevated (more than double) and the A:G ratio became less than normal as shown clearly in another table retained in our records. Similar observation was reported by Mayama (10) while studying the electrophoretic distribution of serum proteins in leprosy. His report indicates that α and β globulins were found to be elevated but the γ globulin was markedly raised while there was a drop in the albumin fraction. But no attempt was made by him to correlate between haemagglutination titre and globulin fractions.

The investigation reported herein shows that with the increase in the globulin fraction there is a simultaneous increase in the haemagglutination titre in 81 per cent of the leprosy cases studied. The low titre value in the rest (19 per cent) of the leprosy cases may be due to some reasons which need further investigation for such low value, although there is an increase in globulin fractions. So it will not be unreasonable to say that there is a correlation between the increase in haemagglutination titre and globulin fractions in this disease. The result appears to be consistent with the view that haemagglutination titre is an index of antibody formation and that antibodies are modified globulins (¹¹).

SUMMARY AND CONCLUSION

Haemagglutination reaction of sera of 32 bacteriologically positive and negative leprosy cases was studied and the protein fractions of their sera were investigated by paper electro-phoresis.

A decrease in albumin and an increase in globulin were demonstrated. Albumin-globulin ratio was less than one. A correlation between the increase in haemagglutination titre and globulin components of the serum proteins in leprosy cases was observed, these data have been statistically verified and found to be significant.

ACKNOWLEDGEMENTS

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Abstracts

Paul Brand and his Mission. Healing and the Pursuit of Pain at a Hospital in India. N. COUSINS, Saturday Review, New York, Oct. 3, 1964, pp. 21–24 and 51.

The author gives a particularly appealing and informative article on Dr Paul Brand and his wife.

Paul Brand is Director of Orthopaedic Surgery at Christian Medical College, Vellore, S. India, and Mrs Brand is an ophthalmologist. Dr Paul Brand went to Vellore as a young man in 1947 and his wife joined him there a year later. Together they make up one of the most remarkable husband-and-wife teams in the world today. Dr Paul Brand has restored the use of their extremities to thousands of leprosy patients. Dr Margaret Brand has saved thousands of leprosy patients from blindness. Both of them teach at the medical college, undertake important research, and work at the hospital and in field clinics.

Dr Paul Brand's main purpose in coming to the Christian Medical College and Hospital in Vellore in 1947 was to explore how he might apply his highly developed skills in the reconstructive surgery of the hands to the special problems of leprosy patients. He began on the problem of 'claw hands' and was soon highly successful, but soon he moved on to the total problem of leprosy. He soon found from his reasearch that 'leprous tissue' as a cause of deformity was unimportant compared to a loss of pain sense and defective sensation generally. The bacillus of leprosy killed nerve endings, but the flesh itself was indistinguishable from normal tissue. The importance lay in the lack of the warning and protective influence of pain, as Prof. Brand found in an encounter with a boy leprosy patient who forced open a door at the expense of a wound, when Prof. Brand himself had abandoned the same task as dangerous. Dr Brand reasoned that leprosy patients lost fingers and toes as an ultimate result of damage to the part from injury and consequent sepsis. He observed leprosy patients as they went about their daily tasks and soon obtained convincing evidence that this idea was correct. He soon found that classes in preventive care were highly productive of undamaged hands and feet. One mystery, the continuing disappearance of digits, was now traced to the intervention of the rat, who destroyed insensitive hands, and devices were developed to protect patients from rats, with remarkable success. He next investigated the collapse of noses and found that the basis of this was the effect of the leprosy bacilli on the delicate membranes inside the nose. This resulted in severe contraction of the membranes and the nose was drawn in towards the head. Brand therefore reconstructed many noses successfully from the inside. The noses could be pushed back into place. In noses with loss of cartilege, insert cartilege grafts or acrylic resins might be needed. Blindness, the most serious affliction of leprosy patients, was long thought to be a specific manifestation. But here intense study at Vellore caused this idea to be questioned and blindness was found to be a bye-product of vitamin A deficiency, and destruction by paralysis of the protecting mechanisms

of the eye. Dr Margaret Brand was very active in preventive and reconstructive surgery of the eye and in removing cataracts, and her operation list was of considerable volume, both in the hospital and in the clinics in the villages. Eye ulcerations were also traced to lack of protection of the eye by natural washing, and various reconstructive and plastic operations get the eyelids working protectively once more in a restored 'blink' and washing of the eye surface. The actions of certain muscles of the jaw were transfered to the eyelids.

Hand in hand with these practical measures the fact that leprosy is eradicable was taught, and demonstrated, and for the medical and functionally cured psychological rehabilitation was studied and taught. By job-training, self-respect as a citizen is given back to the patient.

The core of the whole surgical revolution is giving back the invaluable sense of pain and giving back function as far as possible, and in rehabilitating the patient by practical measures, but above all by research into the facts, and understanding of the patient as an individual.

Notes Concerning Dermatoses in our Countries:

Leprosy. M. EL ZAWAHRY, Journ. of the Egyptian Med. Assoc., 1964, 47, Nos. 11 and 12, p. 1157.

The author deals with common dermatoses of Egypt, and includes a brief description of leprosy.

He states the endemic nature of leprosy in his country, and mentions that he met III patients in one year, and that child leprosy is common, which is serious for the survival of the endemic. Tracing leprosy patients to the source of infection is the only way to eradicate leprosy in a community. He finds lepra reactions more common than in the past, perhaps due to the wide use of the sulphones. He recommends more advanced therapy, and mentions Ciba-1906 because of its safety and efficiency and absence of side effects, and Thiosemicarbazone because with it reactions are minimal. Isoniazid and streptomycin he found disappointing in therapy. Anti-tuberculous treatment can be given without danger in presence of leprosy. In an endemic area BCG is helpful in immunization of contacts against leprosy. Corticosteroids are of value and may be life-saving in reactions of leprosy, but the reactive state is difficult to extinguish entirely.

Fixed Eruption in Deeply Pigmented Subjects: Clinical Observations on 350 Patients. S. G. BROWNE, Brit. Med. Journal, Oct. 1964, 2, pp. 1041-1044.

The author, who is director of the Research Unit of the Leprosy Service, Uzuakoli, Nigeria, found primary sensitization mainly by dapsone and phenolphthalein to fixed eruptions in deeply pigmented African subjects. The fixed eruption, with typical discrete lesions undergoing recurrent exacerbation, merges imperceptibly into a diffuse type of post-inflammatory hypermelanosis after a widespread itching papular eruption. The more diffuse the hypermelanosis, the less marked is periodicity in the signs of exacerbation of the papular lesion.

Drugs incriminated in the sensitivity to the fixed eruption; 254 cases of dapsone, 13 cases of polysensitivity set going by dapsone, three cases of DDSO, two cases of Ciba-1906. There were 78 cases associated with drugs other than anti-leprosy drugs. These were 46 of phenolphthalein, nine of unidentified injections and indigenous purges, five of acriflavine, four each of emetine hydrochloride, acetylarsan, neoarsphenamine, sulphonamides, and amodiaquine, one case of polysensitivity following primary sensitization with chloroquine, and one each of iodide, penicillin, and mepacrine. Antileprosy drugs as well as phenolphthalein enter into wide use in Nigeria. Figures from Yakusu in the former Belgian Congo from 5,349 patients under treatment for leprosy, 160 or 3 per cent of them had fixed eruptions caused by dapsone and solapsone. In 300 patients at Ibadan, Nigeria, Harman found 3 per cent with fixed eruptions. In South Africa, Marshall in 1963 found fixed eruptions induced chiefly by phenolphthalein and the sulphonamides.

The polar types of leprosy, tuberculoid and lepromatous, are parallel in a certain way to the two polar types of fixed eruption.

Transmisión de la infeccion leprosa a animales de laboratorio bajo condiciones dietéticas especiales

(Transmission of the leprosy infection to laboratory animals under special diet). M. BERGEL, Acta Leprologica, April-Sept. 1964, No. 17 and 18, pp. 33-38, 4 figs.

Dr Meny Bergel, of the Leprosy Research Laboratories, Rosario, Argentina, relates his experience with the inoculation of M. *leprae* into rats and mice during the past few years. He used males of rats and white mice of the age of 20 days. The inoculum was obtained directly from untreated lepromatous or borderline patients, and the inoculum was used immediately after being obtained or at the most after 24 hours of refrigeration. The site of inoculation and dosage were in the rat 0.10 ml. intratesticular and 0.03 ml. in the mouse. In the plantar cushion of the rat the dose was 0.05 ml. and in the mouse 0.025 ml. In addition grafts of lepromata of an approximate size of 1 to 2 mm. were introduced surgically under the skin in the right flank of the mouse.

The special dietetic regime was added to standard diet (pieces of compressed vegetables dehydrated and natural water ad lib.) and consisted of five slightly varied diets, namely (1) a semi-synthetic diet with a low content of Vitamin E, that is industrial casein 23.8, powdered brewers yeast 8.9, mineral salts 3.0, maize starch 48.9; crude linseed oil was added, 15 to 20 per cent; (2) a semisynthetic diet similar to the first but with the addition of 15 per cent of cod liver oil; (3) this diet was also like the first with the addition of 15 per cent of an oil made up of pure ethyl esters of linoleic 2/3 and linolenic 1/3 acids, in a very marked state of rancidity with a large content of peroxides and an iodine index of about 13; (4) the semisynthetic diet above mentioned with addition of 20 per cent of crude linseed oil containing chemotherapeutic compounds such as DDS to the amount of 0.5 to 1 per thousand and thioureas in the same proportion; (5) the drinking water of some of the animals contained silver nitrate (0.5 to I per thousand) ferrous gluconate (2.5 to 5 per thousand) and potassium iodide (0.5 per thousand). The water to which silver nitrate was added was distilled water so as to avoid the precipitation of the silver by the chorides.

All the animals were inoculated between 20 and 30 days of age. During the experiment (a) Some of the inocula, and organs in which *M. leprae* developed were sown in the Lowenstein-Jensen medium. (b) An integral lepromin was prepared in cases where transmission in series of *M. leprae* was attempted and also in some other cases. This lepromin was tested against lepromin of human origin on lepromatous and tuberculoid leprosy patients, as well as in apparently healthy patients. (c) Using the methods of Hilson, Elek and Hanks bacillary counts were made. (d) Baciloscopic studies were made of the inoculated area, regional glands, spleen, liver, etc. (e) Histological studies were made. There were control groups for each group of inoculated under special dietetic conditions.

The testicular inoculation of M. *leprae* in rats fed on a prooxidant diet (added linseed oil 20 per cent and 1/1000 silver nitrate in the water) produced a marked development of the germ which was not evident in the control animals on standard diet. The growth of M. *leprae* gave rise to an infiltrate of varying density in the inter-tubular spaces of the testis, and sometimes to the formation of rounded or ovoid granulomata containing bacilli. Inoculation of this material into other rats kept on the same dietetic conditions obtained successful passage. Integral lepromin obtained from the testes behaved like a lepromin of human origin.

When the diet was more pro-oxidant, namely containing 15 per cent of cod liver oil and 0.5/1000 of silver nitrate in the drinking water, a very marked growth of *M. leprae* was produced.

The addition of DDS (0.5 per thousand) and thioureas (0.5 to 1 per thousand) to pro-oxidant diets, inhibited the growth of M. *leprae* inoculated into the testes of the rat. This fact became evident on the third month after inoculation, compared with control animals.

It was found that M. leprae kept for 2.4 hours in refrigeration prior to inoculation kept viable on being inoculated into the testes of the rat nourished on a pro-oxidant diet (with 20 per cent linseed oil and 1/1000 silver nitrate). In the mouse the testicular inoculation of M. leprae using the pro-oxidant diet (20 per cent linseed oil added and 1/1000 silver nitrate) had a clear development of the bacillus in comparison with control animals. Intravenous, subcutaneous, and intra-peritoneal inoculation in mice on pro-oxidant diets obtained inconstant development of globi in the spleen, between the fourth and tenth month after inoculation. The surgical grafting of a piece of leproma under the skin of the flank into mice on the abovementioned pro-oxidant diet resulted in the formation of a small foreign body granuloma, in which the original graft lay in a necrobiotic state. In this necrobiotic zone as in the surrounding connective tissue acidfast bacilli were found, mostly homogeneous and sometimes forming enormous bacillary masses. Part of the fatty tissue adjacent to this granuloma showed a cellular infiltrate with a great number of bacilli, and some of the adjacent nerves were invaded by the bacilli.

On the inoculation of M. leprae in the plantar cushion of the mouse according to the technique of Shepard the author noted that when a high count of bacilli was inoculated practically the development of the bacilli was not obtained and they slowly diminished up to six to eight months after inoculation. This occurred in mice on

standard diet as well as pro-oxidant diet. When the inoculation was small (about one million bacilli or less), a development occurred at the end of six to nine months. In the pro-oxidant animals this produced a well-delimited granuloma abundant in bacilli. In a certain number of animals inoculated when on a standard diet a diffuse infiltration resulted and a regular growth of M. leprae. This is much more marked in the pro-oxidant mice, and the granuloma is very marked and well-delimited, but this also only occurs in a certain number of the inoculated mice. When the pro-oxidant diet has added 2.5 per 1000 of ferrous gluconate, a much greater development of M. leprae is obtained. When the diet includes 0.5 per thousand there is an exuberant development which surpasses all other diets. The result obtained from 15 per cent cod liver oil surpasses that obtained from 20 per cent linseed oil, perhaps because there is less tolerance to the latter.

The diet with the ethyl esters and high rancidity and iodide index completely inhibits the development of *M*. *leprae*, as when DDS is added. In fact the mice of this type develop a syndrome of fatty acid deficiency with testicular atrophy, alopecia round the facial orifices, and marked segmentation of the tail. It seems that essential fatty acids are necessary to the development of *M. leprae*, which is supported by the fact that the diets with a high content of unsaturated fatty acids favoured the development of the bacilli.

The author states that he never noted macroscopic changes nor increase of size in inoculated organs in the rats and mice in the dietetic conditions of the experiment.

The author appends a graph which shows the marked effect in inoculation when on pro-oxidant diet, compared with standard diet and with control groups, all at nine months after inoculation.

Effect of Environmental Temperatures on Infection with Mycobacterium marinum (balnei) of Mice and a Number of Poikilothermic Species. Clark, H. F. and Shepard, C. C. Nov. 1963, *J. of Bacteriology*, 86, 5, pp. 1057-1069.

Mycobacterium leprae (Shepard 1960) and two cultivable mycobacterial species, namely M. marinum (M. balnei) and M. ulcerans (Fenner 1956) grow preferably in the foot-pad of mice, this presumably due to its low temperature. The two cultivable species grow on artificial media at 31° to 35°C, which is less than the deep body temperature of mice. The slow growth of M. leprae in the mouse foot-pad and the low yields of bacilli have limited the range of experiments. It seemed possible that the rate of growth and yield of bacilli in the mouse might be improved by altering the temperature of the mouse environment, and other

animals with imperfect or absent temperature-regulating mechanisms might yield a more favourable result when placed at proper temperatures. The authors therefore inoculated M. marinum peripherally and systemically into mice and a variety of mammals and cold-blooded vertebrates held at different environmental temperatures. Tables 3 and 4 give a great deal of information about the poikilothermic animals used in this experiment, and Table 2 gives details of inoculation of M. marinum in mice maintained at different temperatures. For inoculations in the foot-pad of mice, the optimal temperature was 20 °C. In intravenously inoculated mice there was gross peripheral spread of the bacilli and lesions. The generation time of the bacilli was about 15 hours, which is roughly thrice that of M. marinum in bacteriological medium. Susceptiblity to M. marinum is very widespread among poikilothermic animals (alligator, turtles, salamander, chameleon, snakes, frogs, etc.). Bacillary multiplication could be obtained very consistently in small species and in the young of larger species. Natural conditions of transmission of infection by M. marinum were detected, e.g. tadpoles to tadpoles in water, minnows to tadpoles in water. The use of poikilothermic animals in the study of the effects of temperature on infections has definite advantages, since the temperature of the tissues is as easily adjustable as it is for in vitro systems. Making of cell cultures is easily done, and can be maintained for long periods. Of the poikilothermic animals many are too difficult to obtain, or do not live long under laboratory conditions. For growth in the mouse foot-pad, about five months of observation are usually needed.

The author concludes by mentioning sound evidence for assuming the identity of M. marinum and M. balnei, with priority to the former name.

Localização epithelial do Mycobacterium Leprae (Localization of *M. leprae* in the epithelium). H. Seabra Santos, *Rovisco Pais*, April-June 1964, **3**, 9, pp. 25-28, 5 figs - 2 of which in colour.

The author describes the occurrence of the bacilli of leprosy in the outer sheath of a hair, and not in the neighbouring epidermis of a patient 19 years of age. She had otherwise violaceous infiltration of the forehead, face, and pavilions of the ears, a diffuse discrete infiltration of the hands and forearms, and thickening in both cubital nerves. There were also rounded violaceous macules with ill-defined outlines in both buttocks, lateral aspect of the left hip, and medial aspect of the right hip.

The author thinks that the leprosy bacilli in the hair sheaths could be in part responsible for the hair atrophy and hair loss which occur in leprosy.

Reports

Seminar on the Care of the Foot in Leprosy 17th to 21st August, 1964

The first seminar ever to be held devoted exclusively to the study of foot problems in leprosy was opened at Oji River on 17th August by the Area Superintendent, Dr A. Azike. Nineteen physicians and surgeons from three Regions of Nigeria, three physiotherapists and a number of Nursing Sisters took part.

Papers were read on Surgical Anatomy, on Gait, Wound Infection, Peripheral Nerve Injuries and Joint Neuropathy by Gordon H. Grant, F.R.C.S., of Victoria, British Columbia; on Surgical Anatomy, Gait and Skin Grafting by Miller O. A. Jaja, F.R.C.S., M.CH. (Orthopaedics) of University College Hospital, Ibadan, and on Neuritis in Leprosy by Dr Victor Smith of Kano. Miss Maureen Skelly, M.C.S.P. of Ikpene Obom demonstrated methods of preand post-operative assessment and of physiotherapy and Dr W. F. Ross showed cases illustrating methods of ulcer control (including footwear) and treatment in use at Oji River. Later, Dr Ross demonstrated a series of cases of peripheral neuritis and a series of cases and their X-rays illustrating bone changes typical of leprosy. Dr Priestman of Mongu, Dr Smith and Dr Ross also demonstrated various types of prostheses. Surgery was shared between Messrs Grant and Jaja, Dr Esther Davies of Ikpene Obom and Dr Ross. The 12 cases demonstrated included all the major types of deformities of the foot seen in leprosy.

Vigorous and informed discussion took place during the surgical and clinical demonstrations and in the evenings. Discussions on neuritis, on neuropathic bone changes and on therapy were especially valuable. During the seminar, it was agreed that an attempt should be made to set up a Leprosy Research Association in Nigeria so that members could combine in clinical studies to attempt to solve some of the outstanding problems in this field. It was also agreed that there is an urgent need for training programmes in Nigeria to provide physiotherapy aides, shoe makers and brace makers for every Settlement and that a study should be made of the possibility of training occupational therapy aides also. The proposal that a similar seminar on the 'Care of the Hand' should be held about two years hence was carried unanimously. This itself is eloquent testimony of the fact that all the participants have found this seminar to be of value and would like to repeat the experience. W. F. ROSS

Thirty-fourth Annual Report of Lake Bunyonyi Leprosarium 1963-64

Annual reports on the work of long-established leprosaria may vary very little from year to year, although major effects of the work done may be clearly seen when they are assessed at longer intervals. One was reminded of this when thinking of, and comparing with, the making of maps. In depicting sea-bound coasts that suffer gradual erosion, cartographers can only show marked changes in the outline after a sufficient number of years have elapsed since the previous drawings were made. Looked at in this light it might well be claimed that, under the good hand of God, this Settlement during the 30 odd years of its working has been able to make a considerable 'dent' in the incidence of leprosy in Kigezi. Although the population of this District has almost doubled during that time (and conceivably the numbers of sufferers from leprosy were added to also), the estimated total of between 3,000 and 4,000 cases of leprosy has been reduced to 300 or 400 – literally a decimation – that is, of course, excluding our present patients in the leprosarium. Over 2,500 patients have been registered with us for longer or shorter periods of treatment. Many, unfortunately, have taken themselves off before they should have done so, for one reason or another, but this is not surprising in view of the usually lengthy stay that is necessary to effect 'cures' from this stubborn and often perplexing disease, which shows many variations though largely conforming to three or four major types. However, through the years there has been a steady output of 'arrested' or

'cured' cases (whichever term is favoured) either 'with' or 'without' deformity. We are glad that the latter greatly outnumber the former, and this is especially so since the introduction of the sulphone drugs. These are far more potent than anything in use previously, and are almost universally accepted as standard treatment, having revolutionized the whole outlook for the unfortuante sufferers from this disease.

Looking at our own figures, great encouragement can be derived. In 1950 for example there were 850 active cases under treatment resident on the Island, with a total population of over 1,000, so that we were terribly, but unavoidably, overcrowded. Today there are about 200 requiring treatment, mostly in-patients, while about 50 others are retained, being crippled, blinded, or otherwise incapacitated and needing care or assistance of one sort or another. These for the most part came too late in the course of their infection to be saved from such calamitous consequences.

With these comparisons in mind, and conclusions that may be drawn from them, we proceed to give the report for the 12 months ending 30th June, 1964.

Numbers In-patients 176 on 1st July and 173 on 30th June.

Out-patients, starting with 25, we ended with 35.

Cured, but crippled and retained, 51.

Cured, and retained as staff, 13.

Discharged Cured and sent home, 30; another 29 cured but under observation.

Admission of new cases Thirty-three, two being children under 14, now unusual.

Deaths Six patients have died, three being 'arrested' cases, and three others.

Path. lab. examinations 4,456.

General O.P. treatments for residents 6,371.

Staff Our European Staff has been depleted by the loss of Sister Marguerite Barley, who had to leave for family reasons and may not be able to return. Some non-infected and better educated African Staff have joined us, and the standard of work has been improved. Some small rises in pay have been made possible, although the rate is admittedly too low.

Housing It has been possible to make some improvements in staff housing, as well as that of patients. A completely new house with six good-

sized rooms, plus kitchen, has been built for one of our senior workers with a large family, for the cost of about £750, drawn from the Asker Legacy which was previously deposited with the Mission in England for any such needs.

Food and fuel supplies have been well maintained, and the supply of water by the windmill pumps has continued most of the year.

Finances We are grateful to the Uganda Central Government for renewing their annual grant at the same figure, as also the Local Governments, although the latter gave us a temporary shock by omitting provision for the second half of 1963, when they changed their financial year from July to June, to January to December each year. However, after some representations, this has been either restored or at least promised. We are also grateful to the Mission to Lepers and the British Leprosy Relief Association* for their continued help, while Christian praying and working helpers in the home countries have contributed most generously.

Out-patient department, where non-leprosy patients from the villages and kraals on the hills round the Lake are allowed to come daily, has had a busy year. Total attendances amounted to 10,872, to whom 4,555 injections were given, and 421 had teeth extractions.

Whooping cough prophylaxis During three months in 1963 a mass campaign against whooping cough was carried out in our O.P.D. With vaccine supplied by the Government over 2,000 children of five years and under were brought for injection of three monthly doses. With very fair co-operation by the local chiefs, over 60 per cent of these attended the three times. *CHURCH* and social activities have been continued through the year, and we would express deep gratitude to GOD for all His many mercies.

> R. C. PARRY Medical Superintendent

*The details of Lepra special grant for a Sterilizer are given in the Government Financial Report.

Book Review

Chemotherapy of Tuberculosis, 1964, of V. C. BARRY,

D.SC. (Pp. 281, price sh 79/6 net.) Messrs Butterworth & Co. (Publishers) Ltd, 88 Kingsway, London WC2. Dr V. C. Barry is Director of Laboratories, Medical Research Council of Ireland. Out of his wide experience and active research he has published this study of the chemotherapy of tuberculosis and all leprologists will be greatly interested in this author's account of the position in tuberculosis. The author has followed the plan of giving ten chapters, each of which is written by an expert in his own field.

It begins with description of the Constituents of Mycobacteria written by J. Asselineau of Toulouse and E. Lederer of Paris. The practical subject of Bacterial Pathogenicity and Chemotherapy is dealt with by H. Bloch of Basle. V. C. Barry himself deals with the Development of the Chemotherapeutic Agent for Tuberculosis. G. Meissner of Borstel, Germany, gives next a valuable account of the Bacteriology of the Tubercle Bacillus. F. Winder of Dublin deals closely with the Antibacterial action of Streptomycin, Isoniazid and PAS, and M. L. Conalty of Medical Research Council of Ireland, provides a very useful guide to the Methods of Preclinical Evaluation of Antituberculosis Drugs. G. Canetti of Paris considers Host Factors and Chemotherapy of Tuberculosis, and N. Rist of Paris describes the important question of the Nature and Development of Resistance of Tubercle Bacilli to Chemotherapeutic Agents. John Crofton of Edinburgh provides a valuable Clinical Evaluation of Antituberculosis Drugs and J. R. Bignall of Brompton Hospital closes the book with a study of Current Status of Chemotherapy in Practice. All writers give generous appropriate references at the end of each article and there is a good index.

Of particular value to leprologists is V. C. Barry's description of the Rimino Compounds. On these he speaks with great authority. Particular attention of leprologists is directed to his account of the effects of B 663 in both tuberculosis and leprosy, pp. 56-57.

The book is perhaps best enjoyed by chemists and biochemists, but all who deal with the therapy of the two diseases should possess and study this book.