Editorial

COMPLICATIONS OF TREATMENT WITH CLOFAZIMINE (LAMPRENE: B663)

Much has been written on the subject of this dye since Browne and Hogerzeil (1962) first reported its good effect in the treatment of leprosy, and, as regards its side effects, most are by now well known. These include red-brown pigmentation of skin and conjunctiva with darkening of skin lesions; red colouration of urine, stools, sputum and sweat; dryness of skin, particularly of forearms and lower legs, which may progress to typical ichthyosis; and, less commonly, irritation of skin lesions. The side effect of clofazimine which is less well known, and which has been highlighted in the paper by Plock and Leiker which appears in this Number of Leprosy Review, is its effect on the gastro-intestinal tract. The first reference to this came from Williams *et al.* (1965); of 3 patients treated with the drug, one developed diarrhoea and colicky abdominal pain, and one other patient experienced malaise, anorexia and weight loss, but no abnormalities were detected on x-ray examination. Atkinson *et al.* (1967) reported that a patient of theirs, after several months of treatment, developed anorexia, epigastric pain and occasional vomiting, followed by marked loss of weight. Tests for malabsorption were negative, but x-ray examination revealed coarsening of mucosal pattern and segmentation of barium in ileum and distal jejunum. A specimen of jejunum was obtained by biopsy and showed a normal mucosal villous pattern and moderate numbers of plasma cells in the lamina propria. In addition, red crystals were seen in the lamina propria and were identified by the ultra-violet spectroscope as clofazimine crystals. Pettit *et al.* (1967) recorded that one of their patients complained of intermittent diarrhoea and upper abdominal pain during the third and fourth months of treatment, but was able to complete the 6 months trial without interruption. Inkamp (1968) treated 18 patients with 200 mg of clofazimine daily and noted that 3 patients developed diarrhoea; one after 3 weeks, one after 7 weeks, and the third after 11 months. Helmy *et al.* (1971) treated 10 patients with 300 mg daily given as a single dose, and 2 patients experienced nausea, vomiting and epigastric pain early in the course, but their symptoms settled when the daily dose was divided. Schulz (1971) treated 123 patients with clofazimine and 3 developed abdominal symptoms consisting of pain and bowel irregularity severe enough to stop treatment. They had been treated for 12, 13 and 18 weeks respectively, and the maximum daily dose was 300 mg in 2 cases and 400 mg in the third. Weight loss was so marked in one patient that he was admitted to hospital, but all routine investigations, including x-ray examination, were negative; jejunal biopsy was not done. He recovered soon after the drug was stopped. The other 2 patients subsequently tolerated clofazimine in reduced dosage over several months, while in 10 other patients who complained of transient abdominal pain and nausea in the early stages no

alteration in treatment was required. In a series of 120 patients treated by Karat (1975) 2 suffered from recurrent colicky abdominal pain after 6 months and 18 months respectively. Barium meal studies showed narrowing of the terminal ileum and dilatation of proximal loop. There was no change in the absorptive functions of the small intestine. At laparotomy about 6 inches of terminal ileum appeared thickened and oedematous, and some enlarged mesenteric lymph nodes were found. Histological examination of these nodes and of terminal ileum showed a non-specific granuloma characterized by foreign body giant cells and lymphocytes, together with crystals of clofazimine. No acid-fast bacilli were grown on culture. Clofazimine was withdrawn and the symptoms cleared up in 8 to 10 weeks. Desikan *et al.*, (1975) have reported autopsy findings in a young Indian woman who had suffered from lepromatous leprosy complicated by severe lepra reaction and nephrotic syndrome. The story was that prednisolone had failed to control the reaction so clofazimine was added to her treatment, 300 mg daily, but had to be stopped after 4 months because of diarrhoea which had not responded to reduced dosage. She died a month later, and post-mortem examination revealed a striking colouration of all tissues within chest and abdomen, the colour varying from orange-red to brick-red. There was congestion and oedema of the mucosa of small and large intestine, more pronounced in the former, and histological examination of mucosa and submucosa showed cellular infiltration and oedema together with clofazimine crystals. Similar crystals were also present in liver, spleen and lung. Another finding was widespread amyloidosis, and the fact that the adrenal cortex was seen as a mass of amyloid material confirmed that death had been due to adrenal failure. Harman (1975) has given me details of a Burmese lady who came to England in 1967, was found to be suffering from lepromatous leprosy the following year, and was treated with dapsone. In 1969 treatment was changed to clofazimine because of continued type 2 lepra reaction (ENL reaction), and when she moved to Bristol she came under Dr Harman's care. Clofazimine was continued, dosage varying between 100 and 600 mg daily, and between March 1972 and May 1975 she lost weight and suffered from recurring anorexia, nausea, dirrhoea and abdominal pain. Many investigations were carried out during this time, but failed to establish a diagnosis. Clofazimine was stopped in May 1975 and her gastro-intestinal symptoms improved, but she continued to lose weight (from 38 kg in May to 27.5 kg in September). On 9 September she was admitted to hospital with severe gastro-intestinal symptoms, and 5 days later she died. The cause of death was considered to be acute electrolyte imbalance. At autopsy the typical pigmentation of viscera was seen, and crystals of clofazimine were found in the lamina propria of the small bowel. Mesenteric nodes could not be identified as they were replaced by necrotic brown slime.

One of my patients has demonstrated that clofazimine crystals can be found in mesenteric lymph nodes nearly 4 years after stopping the drug. He is an adult male under treatment for lepromatous leprosy, and clofazimine therapy was instituted in March 1967 because of prolonged type 2 lepra reaction. He continued on the drug until December 1971, a total period of 4 years and 9 months, dosage varying from 100 to 200 mg daily for the first 3¼ years, reducing to 100 mg every alternate day for the next 12 months, and to 100 mg twice a week for the last 6 months. During this time all skin smears became negative, and in December 1971 treatment was changed to dapsone. In October 1974 he began to suffer from diarrhoea and epigastric pain which persisted in spite of various

symptomatic treatments and replacing dapsone by thiambutosine. Stool examinations and x-ray investigations were negative. By October 1975 his gastro-intestinal symptoms were so distressing that a laparotomy was performed, and at operation there were no pigmentary changes in the abdominal viscera and the intestine appeared normal. Mesenteric lymph nodes were enlarged, and one was removed for histological examination together with a small piece of distal jejunum. Dr D. S. Ridley reported as follows:

"*Jejunum:* The histology is within normal limits except perhaps for an excess of mucus secretion. *Mesenteric lymph node:* This shows sinus catarrh. There are some large foamy macrophages heavily loaded with ceroid pigment which is a feature of clofazimine treatment. It is impossible to identify bacilli in the macrophages because of the pigment. Cryostat sections show dense deposits of clofazimine crystals."

Acknowledgements

I would like to thank Mr A. G. A. Cowie for performing a laparotomy on my patient, Dr D. S. Ridley for his histological report, and Dr R. R. M. Harman for supplying me with a case-history of his patient.

W. H. Jopling

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Study of Sulphone Resistance in Leprosy Patients in India

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Studies were undertaken to confirm the occurrence of resistant strains of *Myco. leprae* in leprosy patients who fail to respond to treatment with dapsone. In the first 3 years, 39 patients who had highly active disease despite a long history of treatment were selected from our outpatient clinic. A suspension of bacilli from an active lesion was injected into the foot pads of a group of normal CBA mice. The mice were then fed varying doses of dapsone in the diet for several months. At harvest, multiplication had occurred in the presence of high doses of dapsone in 12, at low dosage in 7 and only in the control group in 14. There were 6 failed experiments. This demonstrates that 19 patients harboured *Myco. leprae* to some extent resistant to dapsone.

Observations on the clinical manifestations and subsequent progress are made and compared with reports from other centres.

Leprosy patients who fail to respond to adequate treatment with sulphones have been well known in India for several years (personal observations). However, they were not documented due to lack of laboratory evidence to confirm these findings beyond reasonable doubt. Now that laboratory facilities to grow the organisms in the foot pads of mice are readily available, studies were undertaken to find out and report the occurrence of resistant strains of *Mycobacterium leprae* in India.

Several papers on the emergence of dapsone resistant *Myco. leprae* have been clearly presented from other countries (Adams and Waters, 1966; Pettit and Rees, 1964; Rees, 1967; Jacobson, 1973). Certain patterns of clinical presentation and bacteriological findings of these patients have been evident. In this study it is aimed to identify the sulphone resistant patients and to record their clinical profile and bacteriological findings with a view to elucidate if possible some of their behaviour.

Material and Methods

During the first 3 years of this study cases were selected by careful screening of patients attending the out-patient treatment unit at this centre. The patients report voluntarily for management or are referred for special study from different

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parts of the country. In addition 3 were referred from village clinics in our control area. Thirty nine cases with features suggestive of sulphone resistance were selected. They were selected on the basis of having a high Bacteriological Index despite a fairly long history of treatment with dapsone be it inadequate or irregular. Patients developing histoid features, or an acute exacerbation while on apparently adequate treatment were also chosen. These patients were classified on the basis of clinical and bacteriological examination and confirmed by histopathological examination of skin biopsies in 31 cases.

A careful clinical history including past schedule of DDS treatment and reactional episodes was recorded in each case. Skin smear studies with estimation of Bacteriological and Morphological Indices were done. The lesion with the highest Bacteriological Index and Morphological Index was biopsied for histology and a portion of the skin biopsy was used for animal experiments using normal CBA mice. The processing of the tissue for animal experimental studies was done as reported in our previous studies (Job, 1970; Job *et al.*, 1974). The animals were divided into 4 groups of 6 animals each. One group was fed a diet containing 0.01% of dapsone, another 0.001% of dapsone, the third 0.0001% of dapsone, and the fourth group on normal diet without drugs. At the end of 6, 8 and 10 months 2 animals from each of the groups were sacrificed and their foot pads were harvested and multiplication of *Myco. leprae* assessed.

All patients continued as out-patients after their presenting symptoms subsided. We could not therefore control their subsequent course of treatment sufficiently to correlate this with the results of the experiment in mice. Some of the patients because of the severity of their disease, with chronic reaction or advanced relapse, were started on clofazamine directly after the test was over. Others were continued on dapsone 50 or 100 mg daily until the result of the test was available

Results

In the experiments conducted on 39 patients, 6 were considered to be failures. That is, there was no multiplication of *Myco. leprae* in the foot pads of any mice. Fourteen strains were highly sensitive to dapsone, multiplication being inhibited in all 3 groups fed dapsone in the diet, but with growth in the control group of mice. In 7 experiments there was growth of *Myco. leprae* in mice fed 0.001% and 0.0001% dapsone in the diet, though growth was inhibited in mice fed 0.01% dapsone. In 12 experiments there was multiplication in the foot pads of mice in all groups and therefore the strains of *Myco. leprae* concerned have become resistant to dapsone (Table 1).

Clinically, there were among the 39 patients, 31 of lepromatous leprosy, 4 with borderline lepromatous leprosy and 4 with histoid nodules (Ridley and Jopling, 1966; Wade, 1963). These were evenly distributed among the groups in the experiment as shown in Table 2. In all but 3 cases it is noted that there were active discrete lesions superimposed on old diffuse lepromatous disease. These lesions are described as nodules in 10 of the resistant cases, 12 of the sensitive cases, 6 of the partially resistant and in 3 in which there was no growth. In 2 of the resistant and sensitive groups, and one of the no growth group the lesions are described as raised erythematous lesions or plaques (see Table 3).

The Bacteriological Index (Ridley, 1958) of these lesions was particularly high compared to the surrounding skin and tended to have a raised percentage of solid

TABLE 1

The growth of Myco. leprae *in mice fed varying doses of dapsone*

Number of patients	Growth of bacilli in mice fed on: Control diet	0.0001% DDS in diet	0.001% DDS in diet	0.01% DDS in diet	DDS sensitivity
12	+	+	+	+	Resistant
7	+	+	+	0	Partially resistant
14	+	0	0	0	Sensitive
6	0	0	0	0	Unknown (failed experiment)
Total 39					

TABLE 2

Distribution of types of leprosy among patients tested for dapsone (DDS) resistance

DDS sensitivity	Number of patients presenting with: Histoid leprosy	Lepromatous leprosy	Borderline lepromatous leprosy
Resistant	1	10	1
Partially resistant	2	4	1
Sensitive	1	12	1
Unknown	–	5	1

TABLE 3

Nature of presenting skin lesions among patients tested for dapsone resistance

Dapsone sensitivity	Number of patients presenting with: Nodules	Infiltrated plaques	Not stated
Resistant	10	1	1
Partially resistant	6	–	1
Sensitive	12	2	–
Unknown	3	2	1

rod forms. The distribution of these findings is demonstrated in Table 4. The higher Morphological Index (Waters and Rees, 1962) tended to occur with greater frequency in resistant cases (Table 5).

In most cases the patients mentioned the places where they had received treatment previously and did not know either the drugs or dosage they were given. It is presumed that recognized leprosy centres were using sulphones from

TABLE 4

Bacteriological Index (BI) of the lesion biopsied among patients tested for dapsone resistance

Dapsone sensitivity	Number of patients: BI 2	BI 3	BI 4	BI 5	BI 6	Not available
Resistant	–	1	–	4	4	3
Partially resistant	–	–	4	2	1	–
Sensitive	–	–	1	5	3	5
Unknown	–	1	2	1	1	1

TABLE 5

Morphological Index of suspension used for foot-pad inoculation

Dapsone sensitivity	Morphological Index 0	1-5	6-10	11-15
Resistant	1	4	6	1
Partially resistant	–	5	2	–
Sensitive	2	9	2	1
Unknown	4	2	–	–

1960 onwards. Some patients were quite specific as to the maximum dose they had received and could give many more details. The case records of a few were available for assessment.

A frequently recurring feature in the history of these patients was the occurrence of chronic ENL reaction. This was elicited from 6 patients from whom resistant strains of *Myco. leprae,* were isolated, also from 2 with partially resistant *Myco. leprae,* 5 with dapsone sensitive infection and 4 of the group which had no growth in mice. This complication of the disease had a marked effect on the treatment in every case, causing dapsone to be given either in low dosage or intermittently.

Of the cases harbouring dapsone resistant organisms 5 claimed to have been taking treatment regularly. Four of these had been having treatment for 25 years or more. The fifth had been on low doses of dapsone because of frequent episodes of reaction and had treatment for less than 5 years.

Among patients harbouring organisms resistant to low doses of dapsone, 5 had been taking treatment irregularly. The range of time from start of treatment to the time of test was from 4 to 30 years. Two patients taking treatment regularly also carried organisms resistant to low doses of dapsone. The duration of treatment before test in these patients was 6 and 11 years.

In patients carrying dapsone sensitive organisms 11 had been irregular with their treatment over a time range of 4 to 14 years before the test. Three had been regular with treatment over a period of 15 to 35 years.

In the failed experiment group similarly 4 patients had been irregular with

treatment, the duration of treatment before relapse being 9 to 14 years. Two patients had been regular with treatment for 15 and 20 years.

Of particular interest is a patient who had been taking treatment for 35 years but had discontinued 4 years after becoming skin smear negative. Two and a half years later he relapsed and the organisms were found to be still dapsone sensitive by the test in mice and subsequent progress. On the other hand a patient taking treatment for 6 years and discontinuing on the attainment of smear negativity relapsed 6 months later with organisms partially resistant to dapsone. A third patient who has been an inmate in a leprosy home since 1940 attained smear negativity in 1961. Even from that time he was consistently getting 50 mg dapsone daily. Twelve years later he relapsed with histoid lesions and the organisms recovered were resistant to dapsone.

Follow Up

Patients who are shown to have dapsone resistant *Myco. leprae* are treated with 100 mg clofazimine daily. Of the 12 resistant, 2 are lost to follow up. Ten are showing satisfactory resolution of their lesions and a significant reduction in the Bacterial Index on skin smear of the appropriate sites and a zero Morphological Index.

Of patients with *Myco. leprae* partially resistant to dapsone, 3 have been lost to follow up. Three are being treated successfully with clofazimine, as is the one case who is now taking 100 mg dapsone daily.

In the group with dapsone sensitive infection, 7 are still available to follow up. They are all either on dapsone 50 mg or 100 mg daily. Three are making satisfactory progress. Three are making very slow, or no progress, and one has definitely deteriorated and is still developing new lesions though on 100 mg dapsone. This latter case is being retested.

In the failed group 3 are still being followed up. One case is taking 100 mg clofazimine daily; one, 100 mg dapsone daily and one is on 50 mg dapsone daily. All are making satisfactory progress.

Discussion

While it is apparent from this study that there are no particular clinical features that will identify patients harbouring dapsone resistant *Myco. leprae,* this can be proved in cases of relapsed leprosy, particularly in cases with active nodules and high bacterial positivity, by using the mouse foot pad technique for culturing the organism. It was observed that the nodules may develop quite suddenly over the course of 1 or 2 months. It is hard to imagine that this could happen if the organism is multiplying at its usual rate of once in 12 to 21 days. It is fascinating to consider what factors may be involved in accelerated multiplication in localized lesions in patients who have little or no immunity to the infection.

The result of the test in the mouse foot pad depends very much on a suitable representative biopsy being made of the most active looking lesion. It is possible that the case still deteriorating on dapsone did not have a representative lesion biopsied in his first test.

It is noted that the highest dose of dapsone we used in the mouse experiments was 0.01% which has been shown (Ellard *et al.*, 1971) to correlate closely with the usual maximum therapeutic dose in man of 100 mg dapsone daily. Those with

organisms resistant at the lower doses may yet respond to 100 mg dapsone daily, at least for a time.

The patients on clofazimine who know they are resistant are very careful now to take their treatment regularly. The reason some may not be doing well in the sensitive group may be that they are lulled by the result of the test into a false sense of security, and are still being irregular in their treatment. They are still very much at risk for developing resistance because of the prolonged persistance of viable bacilli.

The results show a tendancy for relapse to be earlier if treatment is irregular. With regular treatment relapse tends to be delayed particularly if the dose of sulphone is high. However, even 50 mg dapsone daily is no protection against relapse with dapsone resistant organisms. Also skin smear negativity is an inadequate test for cure of lepromatous leprosy, for even after a prolonged course of apparently successful treatment a patient may relapse then with sulphone resistant organisms.

The association with reactive episodes is significant only in that it has affected the dose and regularity with which dapsone is prescribed. Now effective anti-inflammatory drugs are available to control reactive episodes, it is no longer necessary to reduce or stop dapsone treatment.

The finding of dapsone resistance among a proportion of patients with uncontrolled or relapsed lepromatous infection is very similar to that reported from other centres. The clinical appearance, past history and subsequent response to therapy is also consistent with what has been observed elsewhere. (Pearson, Rees and Waters, 1975; Jacobson, 1973; Pettit *et al.*, 1966). It is emphasized that the sooner a patient's disease can be controlled with adequate therapy the less risk there is of developing resistance. It may be necessary to consider combined therapy if this complication is to be avoided.

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Studies of the Mouse Foot Pad Technique for Cultivation of *Mycobacterium leprae.* 2. The Relationship Between Incubation Period and Generation Time

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The results were reviewed of mouse inoculation with *Mycobacterium leprae* recovered from 417 skin biopsy specimens. The incubation period (*IP*), the number of months between inoculation and the first appearance of a significant number of AFB in a monthly section, was found to be closely related to the generation time (*G*), the average number of days per doubling. Specimens from treated patients gave larger values of *IP* and *G*, consistent with killing of *Myco. leprae* during effective treatment. Forty-four specimens are described that appeared to provide inocula only marginally sufficient to infect a mouse. The results of this review confirm the validity of the use of the *IP* and *G* as criteria of infectivity of inocula of *Myco. leprae* for the mouse foot pad, and justify the practice of employing both measurements in the conduct of the technique.

Introduction

Two measurements are made in the performance of Shepard's foot pad technique (Shepard, 1960, 1962). One mouse is sacrificed each month for measurement of the "incubation period" (*IP*), the number of months that have elapsed between inoculation of the mice with a small number ($\leq 10^4$) of *Mycobacterium leprae* and the demonstration of acid-fast bacilli (AFB) within 30 to 40 cells in histological sections of the inoculated foot pad tissues. After evidence of multiplication has been noted in a monthly section, a harvest of *Myco. leprae* is performed, usually from the pooled tissues of 4 foot pads. The "generation time" (*G*) is the average number of days per doubling, calculated as if all of the inoculated bacilli multiplied at a constant rate between incubation and harvest.

Both measurements are used in determining the rate at which *Myco. leprae* are killed during treatment of patients with lepromatous leprosy (Collaborative Effort, 1975; Levy *et al.*, 1972; Shepard *et al.*, 1968, 1972*a*, 1972*b*, 1974).

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Usually, both the *IP* and *G* are observed to increase at about the same rate during effective chemotherapy.

Occasionally, however, evidence of multiplication is observed in a monthly section that cannot be confirmed by harvest. And conversely, a harvest sometimes yields evidence of multiplication despite there having been no such evidence in the monthly sections obtained during one year after inoculation of the mice. In order to understand these apparently anomalous results, we have reviewed the data obtained in our laboratory during the past 8 years, and have examined the relationship between measurements of the *IP* and *G* for 417 skin biopsy specimens from which *Myco. leprae* were recovered and inoculated into mice.

Materials and Methods

Since September, 1967, the *Myco. leprae* recovered from more than 500 skin biopsy specimens obtained from leprosy patients have been inoculated into mice in this laboratory. Of these specimens, 417 were selected for analysis because the average inoculum was at least 10^3 but less than 10^4 *Myco. leprae*/foot pad, and because data from both monthly sections and harvests of AFB from foot pad tissues were available.

Recovery of organisms from biopsy specimens, inoculation of mice and harvests of AFB from mouse foot pad tissues were accomplished by published methods (Shepard, 1960; Shepard and McRae, 1968). About half of the foot pad tissues obtained for histopathological examination were prepared by decalcification of tissue blocks cut through the entire foot (Shepard, 1962). The remaining foot pad tissues were prepared by a technique suggested by S. R. Pattyn, Prince Leopold Institute for Tropical Medicine, Antwerp, Belgium, in which the soft tissue was dissected from the metatarsals in a single piece that was fixed and subsequently sectioned.

Results

Each of 417 specimens is represented by a point in Fig. 1, which is a histogram showing the distribution of values of *G* for all values of the *IP* ranging from 4 to >12 months. Because mice were not always sacrificed earlier than 4 months after inoculation, the few specimens showing histopathological evidence of multiplication as early as the third month have been pooled with those yielding an *IP* of four months. Mice were not sacrificed to provide material for histopathological examination later than one year after inoculation. In the 158 cases in which histopathological evidence of multiplication was not encountered within one year after inoculation, a harvest was performed from the inoculated foot pad tissues of all remaining mice to a maximum of 8 foot pads. In addition to the points representing each specimen, the median value of *G* is shown for each value of the *IP*.

As shown in Fig. 1, there appears to be a reasonably linear relationship between the median value of *G* in each distribution and the corresponding value of the *IP*. Because the *IP* is a discrete rather than a continuous variable, this relationship cannot be examined by the linear regression technique. However, one may readily construct the 2 × 2 table shown in Table 1, which demonstrates that the 417 specimens are about evenly divided between those with $IP > 8$ months and those with $IP \leqslant 8$ months. Likewise, the specimens are evenly divided between those

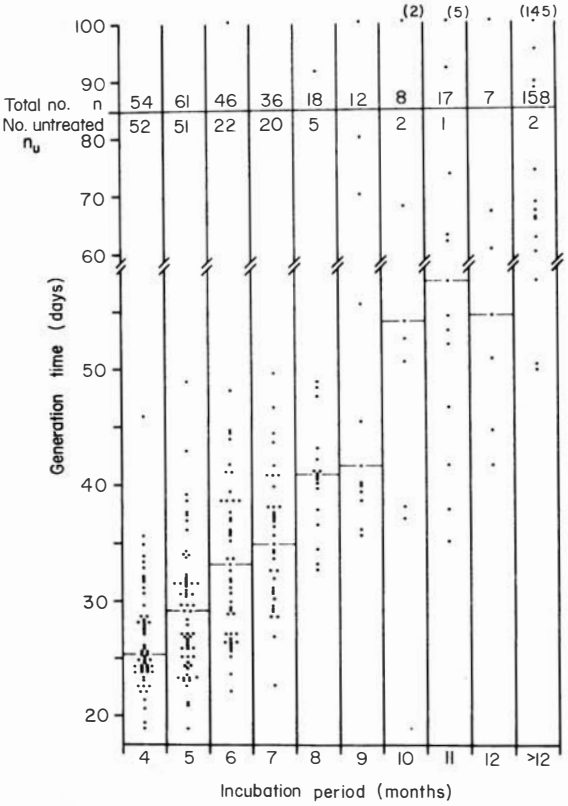

Fig. 1. Relationship of *IP* and *G* for 417 specimens.

with $G < 40$ days and those with $G \geqslant 40$ days. About 95% of the specimens with $G < 40$ days yielded an $IP \leqslant 8$ months, whereas only 14% of specimens with $G \geqslant 40$ days yielded an $IP \leqslant 8$ months. The probability that this distribution of 417 results could have occurred by chance is vanishingly small; *P*, as measured by Fisher's exact probability test (Goldstein, 1964), is about 10^{-70}. Thus, both *IP* and *G* appear to measure the same phenomenon.

Of the 417 specimens, 155 were obtained from untreated patients. The results of these specimens are not distributed uniformly across all of the values for the *IP*, but, as might be expected, represent a disproportionately large share of the specimens yielding smaller values of *IP* and *G*. The distributions of the values of *IP* and *G* yielded by the specimens obtained from untreated patients are shown in Table 2. As demonstrated in the upper panel, only about 3% of the specimens from untreated patients but 75% of those obtained during treatment yielded values of the $IP > 8$ months. Similarly, as the distribution in the lower panel of Table 2 shows, only about 14% of specimens from untreated patients but 77% of those from treated patients yielded values for $G \geqslant 40$ days. The probability that either of these distributions could have been encountered by chance is negligible.

TABLE 1

Analysis of relationship between IP *and* G *for 417 specimens*

		Number of specimens G (days)		
		<40	$\geqslant 40$	Total
IP (months)	$\leqslant 8$	184	31	215
	>8	10	192	202
	Total	194	223	417

Therefore, the distributions of the values for *IP* and *G* obtained from treated and untreated patients are consistent with our expectations: the larger values of *IP* and *G* are associated with the specimens obtained from treated patients, consistent with killing of *Myco. leprae* during effective chemotherapy.

TABLE 2

Distributions of IP *and* G *for untreated and treated patients*

		Number of specimens		
		Untreated	Treated	Total
(a) *IP* (months)	$\leqslant 8$	150	65	215
	>8	5	197	202
	Total	155	262	417
(b) *G* (days)	<40	135	60	194
	$\geqslant 40$	21	202	223
	Total	155	262	417

Of particular interest in this presentation are four categories of results summarized in Table 3, all of which may be explained by inocula containing numbers of viable organisms only marginally adequate to infect mice. Category A includes the 10 specimens shown in Fig. 1 with $IP \leqslant 12$ months and $G > 60$ days but <100 days. All of these specimens were obtained from patients under treatment. Consistent with the large values of *G* are the large values of *IP* and the small numbers of AFB actually counted in each preparation and calculated as the mean value per foot pad. Portions of 6 specimens studied simultaneously in the laboratory of C. C. Shepard, Center for Disease Control, Atlanta, Georgia, or in the Leonard Wood Memorial Leprosy Research Laboratory, Cebu, Philippines,

were found to produce multiplication of *Myco. leprae* in mice. The specimen yielding the median G of 68.0 days gave an IP of 10 months. A harvest of *Myco. leprae* from the pooled tissues of 4 foot pads performed 355 days after inoculation produced an average of 1.86×10^5 AFB/foot pad. Assuming a lag phase of 30 days' duration, the actual doubling time during logarithmic multiplication was 62.3 days if all 5000 of the inoculated *Myco. leprae* multiplied, and 18.6 days if only one infective organism per foot pad was provided by the inoculum. The smaller value is much closer to published estimates of the doubling time of 12 to 13 days (Levy, 1970; Shepard and McRae, 1965), suggesting that specimens yielding large values of G are those providing proportions of *Myco. leprae* infective for mice no greater than 5:5000, because the minimal infective dose is about 5 infective organisms (Levy *et al.*, 1974; Shepard and McRae, 1965).

Category B contains the 13 specimens shown in the right-hand bar of Fig. 1 to yield $IP > 12$ months but $G < 100$ days. Ten specimens were obtained from patients during treatment and 2 from untreated patients; the treatment status of the remaining patient is unknown. Except for the $IP > 12$ months, the results of study of these specimens are much like those of Category A. Portions of 7 specimens were also studied in the Cebu laboratory; 5 yielded evidence of multiplication. The specimen yielding the median value of G in this category gave, of course, $IP > 12$ months. That is, 9 of the 20 mice inoculated with 4.87×10^3 organisms/foot pad recovered from this specimen had been sacrificed during the year following inoculation; not one demonstrated evidence of multiplication of *Myco. leprae* on histopathologic examination of the inoculated foot pad tissue. Because multiplication should have been apparent within one year, one or more of the 9 mice had not received the minimal infective dose. A harvest of *Myco. leprae* performed from a pool of 8 inoculated foot pads 364 days after inoculation yielded a mean of 2.20×10^5 AFB per foot pad. Again assuming a 30-day lag phase and that all of the multiplication in each foot pad proceeded from a single infective organism, the actual doubling time during logarithmic multiplication may be calculated to have been 18.8 days. But it is likely that not all of the inoculated foot pads received a minimal infective dose. If only one of the 8 foot pads had actually been infected, a single infective organism doubling at a rate of once every 16 days through 21 doublings could have produced all of the organisms recovered at harvest. The single infected foot pad would have been diluted by the 7 uninfected foot pads to yield the mean number of AFB/foot pad found.

The eleven specimens comprising Category C were selected from the group of 145 specimens with $IP > 12$ and $G > 100$ (see Fig. 1) because the number of *Myco. leprae* per foot pad calculated from the result of a harvest was greater than 10^4. All of these specimens had been obtained from patients during treatment. Perhaps more informative than the average number of AFB/foot pad is the actual number of AFB counted (the fourth column in Table 3); this number was 14 for 2 specimens, 12 and 10 each for 1 specimen, 7 for 2 specimens, and 6, 4, 3, 2 and 1 each for 1 specimen. The observation of 1 to 3 organisms does not suggest that the *Myco. leprae* have multiplied, whereas the observation of 10 to 14 organisms almost certainly indicates that multiplication has occurred. Portions of 7 of these 11 specimens were studied in Cebu; evidence of multiplication was found for 5 of the specimens—those for which 14, 12, 10 and 4 AFB were actually counted in San Francisco. One of the 2 specimens yielding 7 AFB and that yielding 3

TABLE 3

Specimens with large values of G

Category	No. of specimens	Results of study in San Francisco				Results of study elsewhere	
		IP median range (months)	No. AFB/ 60 fields median range	No. AFB/ foot pad median range ($\times 10^3$)	*G* median range (days)	No studied	No. showing multiplication
A	10	11 / 8-12	36 / 10-110	190 / 49-310	68.0 / 60.7-92.1	6	6
B	13	>12	50 / 15-183	248 / 74-822	66.2 / 49.7-95.2	7	5
C	11	>12	7 / 1-14	19.0 / 11.0-53.0	>100	7	5
D	10	11 / 6-12	0 / 0-7	<9.0 / <2.7-31.0	>100	7	6

organisms did not show multiplication in Cebu. Illustrative of the specimens in this category is the specimen for which 10 AFB were counted in 60 oil-immersion fields. No organisms were encountered in monthly sections during the year following inoculation of mice with 5×10^3 *Myco. leprae*/foot pad. A harvest performed from the pooled tissues of 8 foot pads 378 days after inoculation yielded 4.0×10^4 AFB/foot pad with $G = 126$ days. Assuming that multiplication had occurred in all of the foot pads, the doubling time during logarithmic multiplication may be shown to be 23 days, whereas the doubling time becomes 19 days if all of the enumerated organisms had been contributed by only one of the 8 foot pads. This category appears to represent an extension of Category B.

The fourth category, Category D, contains the 10 specimens with $IP \leqslant 12$ months but $G > 100$ days shown at the top of Fig. 1. All but one of these specimens were obtained from patients under treatment. Seven AFB were counted in the study of the specimen with $IP = 9$ months. A harvest from 8 mice performed 327 days after inoculation of 5×10^3 AFB/foot pad yielded a mean of 3.1×10^4 organisms/foot pad with $G = 124$ days. If all of these organisms had been contributed by one foot pad that had been infected with a single infective organism, the doubling time during logarithmic multiplication would be 17 days. Thus, *Myco. leprae* almost certainly multiplied in the mice inoculated with organisms from this specimen in addition to the mouse sacrificed for histopathological study 9 months after inoculation. No organisms or only one were found in harvests of 2 to 12 mice inoculated with organisms recovered from the remaining 9 specimens. Portions of 7 of these specimens were studied simultaneously in another laboratory; evidence of multiplication was found in 6 of the 7 cases.

Seven of these 44 specimens were studied with more than one harvest. The results of the harvests, shown in detail in Table 4, suggest that inoculation of mice with organisms recovered from each specimen produced irregular infection. Considering the first specimen, for example, the mouse sacrificed after 8 months to provide material for histopathological examination showed multiplication of *Myco. leprae* as did one or more of the 4 mice from which a harvest was made 301 days after inoculation. However, none of the 9 mice harvested later had been infected (that is, multiplication of *Myco. leprae* had not occurred). Similarly, one may conclude that at least 2 mice inoculated with AFB from the second specimen received the minimal infective dose—the mouse yielding the *IP* of 11 months and at least one of the mice used for harvest 379 days after inoculation, whereas none of the four mice from which a harvest was made on day 343 appears to have been infected. The organisms recovered from specimen no. 3 infected the mouse sacrificed for sections at 11 months and at least one of the 6 sacrificed for harvest at day 421, but none of the 8 mice used for harvest on day 378. The AFB from specimen nos 4, 5 and 6 appear to have infected only one mouse in each case.

The results of study of these 44 specimens have demonstrated that: (1) a harvest may yield evidence of multiplication of *Myco. leprae* when monthly sections have not; (2) a section may show evidence of multiplication, whereas harvests do not; (3) one harvest may show evidence of multiplication, whereas one or more additional harvests from the same group of mice may not; and (4) evidence of multiplication may be found in one laboratory but not in a second when portions of the same specimens are studied simultaneously by methods shown to be entirely comparable (Collaborative Effort, unpublished data; Levy *et al.*, 1970). Thus, a specimen yielding $G = 60$ days appears likely to be one

TABLE 4

Specimens with large values of G *harvested more than once*

		Inoculum		Harvest				
No. of specimen	Category	No. AFB/ foot pad ($\times 10^3$)	*IP* (months)	No. days	No. mice	No. AFB/ 60 fields	No. AFB/ foot pad ($\times 10^3$)	*G* (days)
1	A	5.0	8	301	4	10	48.9	91.5
				344	4	1	9.2	>100
				384	5	0	<4.0	>100
2	A	5.0	9	343	4	1	4.5	>100
				379	6	38	210.	70.3
3	A	5.0	11	378	8	1	2.9	>100
				421	6	18	119.	92.1
4	B	5.0	>12	370	8	29	161.	73.9
				426	3	0	<8.4	>100
5	C	5.0	>12	376	8	14	40.1	>100
				457	3	1	7.0	>100
6	D	1.1	10	348	4	1	6.0	>100
				426	4	0	<8.0	>100

containing a proportion of *Myco. leprae* infective for mice no larger than 5:5000. Inoculation of mice with suspensions containing smaller proportions of infective organisms appears to infect the mice irregularly.

Discussion

The purpose of this study was to examine the relationship between the 2 measurements of bacterial multiplication employed in the performance of Shepard's mouse foot pad technique for cultivation of *Myco. leprae.* Review of the results of the study of 417 specimens reveals a close relationship between the 2 measures in the case of 373 specimens (almost 90%). Two hundred thirty-nine specimens yielded $IP \leqslant 12$ months and $G < 60$ days, and 134 specimens yielded $IP > 12$ months and $G \gg 100$ days, suggesting that the 2 measurements deal with the same phenomenon. Moreover, the fact that specimens from untreated patients account for 152 of the 239 specimens (64%) with $IP \leqslant 12$ months and $G < 60$ days and for only 1 of the 134 specimens with $IP > 12$ months and $G \gg 100$ days appears to confirm the validity of these measurements as criteria of the response of patients with lepromatous leprosy to effective antimicrobial treatment.

The remaining 44 specimens were arbitrarily divided into four categories—10 with $IP \leqslant 12$ months and $G > 60$ days but < 100 days; 13 with $IP > 12$ months and $G < 100$ days; 11 with $IP > 12$ months and $G > 100$ days but with harvests yielding $>10^4$ AFB/foot pad; and 10 with $IP \leqslant 12$ months and $G > 100$ days. Of the 44 specimens, only 3 were obtained from previously untreated patients. The 41 specimens obtained from patients during treatment represent 14% of the total number of specimens obtained during treatment. Nine treatment regimens are represented; these 41 specimens accounted for 6 to 21% of the specimens in each regimen, but were not significantly segregated in any one regimen. There was perhaps a relationship between regimen and the duration of treatment at the time these specimens were obtained.

These specimens appear to represent a group intermediate between those yielding unequivocal evidence of multiplication and those yielding no such evidence, providing inocula containing only small proportions of *Myco. leprae* infective for mice. When the proportion is large enough (perhaps some or all of the specimens in Category A), all of the mice receive a minimal infective dose; multiplication is "slow"—i.e., G is large—because more doublings are required for multiplication to reach detectable levels than when a larger proportion of the inoculum consists of infective organisms. An inoculum containing only a marginally adequate proportion of infective organisms may infect mice irregularly. In fact, this has been demonstrated by Hilson in his technique of "proportional bacteriocide" (Holmes and Hilson, 1974), in which the assumption is implicit that one can always detect multiplication if it has occurred. The same assumption underlies the decision to discontinue examination of monthly sections after a year has passed; one year should be long enough for multiplication to have become apparent.

The most problematic of the 4 categories is Category D, which consists of the specimens with $IP \leqslant 12$ months and $G > 100$ days. Do these results indicate multiplication, or may they represent persistence of the inoculum which has been distributed in so fortuitous a manner as to be encountered in a section cut at random through the inoculated tissue? If the latter explanation were true, one would expect to find such specimens early as well as late after inoculation, and

unsupported by evidence of multiplication in a second laboratory. However, the *IP* was 9 months or longer for 9 of the 10 specimens in this category; a second monthly section was found to show numbers of AFB in one case; evidence of multiplication was found in a second laboratory in 6 of 7 cases; and a harvest showed evidence of multiplication although *G* was greater than 100 days in another case. Thus, the demonstration of numbers of AFB in only a single monthly section may be taken as evidence of multiplication despite $G > 100$ days.

This review has provided an opportunity to assess the validity of the criteria applied to the results of mouse foot pad inoculation. Do an $IP > 12$ months and $G \geqslant 100$ days separate those specimens containing *Myco. leprae* infective for the mouse from those that do not? If no harvests had been performed after monthly sections had failed to reveal multiplication of the organisms for 12 months, 13 of the 272 (5%) specimens demonstrating multiplication would not have been so recognized. The results of a clinical drug trial would not be changed by considering these 5% of specimens to have indicated no multiplication rather than irregular multiplication from a marginally adequate inoculum. If the single infected mouse had not fortuitously been sacrificed for histopathological study in the case of the 10 specimens (4%) yielding an $IP \leqslant 12$ months with $G \geqslant 100$ days, these specimens might have been considered not to contain infective *Myco. leprae*; this would not have changed the results of a drug trial.

One may reasonably inquire why, if the two measures of multiplication of *Myco. leprae* yield essentially identical results, both should be performed. The sections are far more economical of mice and of effort, but provide only a qualitative answer. The harvest of *Myco. leprae* from a pool of foot pad tissues provides a more quantitative estimate of multiplication; a small value of *G* indicates multiplication of *Myco. leprae* in all of the tissues in the pool from an inoculum containing greater than a minimal proportion of infective organisms. But harvests are more time-consuming and use more mice, so that one would like to know in advance of the harvest that multiplication had occurred. Therefore, the combined use of both measures appears optimal, using the results of the monthly sections to schedule the harvest. The routine developed by Shepard appears most economical—namely, to sacrifice a mouse monthly for histopathological examination, scheduling a harvest when a section shows multiplication, and considering the mice uninfected without further study if sections show no multiplication for 12 months.

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A Long Term Trial with Clofazimine in Reactive Lepromatous Leprosy

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A report is given on 17 lepromatous patients, all but one steroid dependant because of repeated, serious reactions, treated with clofazimine in dosages of 100-600 mg daily, for periods up to 5 years. In 14 patients who completed 2½ years of treatment the average annual decrease of BI in smears and biopsies was 13% and 14% resp., being somewhat slower than after sulphone treatment (17%). Out of 6 patients who completed 5 years of treatment 5 became negative, one after 4 years, 4 after 4½ years. In some patients, however, the decrease of the BI was slow and unsatisfactory. No evidence of resistance to lamprene was found. No correlation was found between slow response and long period of weaning off steroids or with other complications.

The decrease was somewhat slower in patients with long duration of disease and long duration of previous (sulphone) treatment. In this series of patients the overall long-term reaction suppressive effect was somewhat less than in other trials and not better than in patients treated with 100 mg daily. No correlation was found with duration of disease and bacteriological progress.

In this series an unusually high proportion of the patients complained of abdominal pain, vomiting after medication and some of diarrhoea, to the extent that clofazimine treatment had to be discontinued (7 out of 17 patients).No correlation was found with duration of disease, duration of previous treatment, steroid dependance or sex. The lower frequency of abdominal complaints reported from trials with lower dosages of clofazimine suggest a relationship with dosage. A history in several patients of severe enteritis or dysentery prior to clofazimine treatment suggests that clofazimine acts as an irritant in particular if the intestines have already become irritable by other factors.

The first reports on activity of clofazimine in leprosy (Browne and Hogerzeil, 1962, Browne 1965) have been confirmed by many authors. Several reports, including some on controlled clinical trials (Tolentino *et al.*, 1971) indicate that the antibacteriological activity of clofazimine is of the same order as of DDS. Some studies, however, suggest a somewhat lower activity (Hastings *et al.*, 1969).

The anti-inflammatory properties of clofazimine too, first reported by Browne

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(1965) were confirmed by most authors. Pettit (1967) and Karat *et al.* (1971), however, did not find a significant anti-inflammatory effect using 100 mg clofazimine daily. In other trials (a.o. Leiker, 1970) it was found that although this dosage did not have a rapid effect on reactions, the incidence and severity of reactions in a high proportion of reaction prone lepromatous patients diminished significantly within a year, to the extent that most steroid dependent patients could be weaned of steroids. In other trials with higher dosages of clofazimine (200-600 mg daily) a marked anti-inflammatory effect was found (a.o. Imkamp, 1968, Karat *et al.*, 1970), confirmed in a double blind clinically controlled trial (Helmy *et al.*, 1971). In 2 series of steroid-dependent lepromatous patients, treated with 100 mg and 200-400 mg clofazimine daily, Leiker (1971) did not find a significant difference in the time needed for weaning the patients off steroids. The general impression obtained from the literature is that most patients respond favourably, bacteriologically as well as with respect to the incidence and severity of reactions, but that some patients continue having mild to moderately severe reactions and some patients fail to respond satisfactorily even to higher dosages.

The present study was made to evaluate the long term effect of clofazimine in a

TABLE 1

Complications after clofazimine treatment

Pat.	Sex/age	Duration disease (years)	Previous treatment (years)	Previous reactions	Steroid dependance	Daily dosage clofazimine	Withdrawal steroids after
1212	M35	5	3	+	±	300	5 weeks
970	F30	7	6	++	–	300	2 months
1455	M45	14	14	++	–	200	not
1228	M20	4	3	++	++	300	9 months
220	F35	24	13	++	++	2-300	27 months
914	M35	9	4	++	++	3-400	7 months
1202	M40	11	3	++	++	300	9 months
349	M40	14	9	++	++	300	not
281	F35	18	5	++	++	300	4 months
555	M20	12	9	++	++	300	5 months
1519	M25	3	2	++	++	300	10 months
1000	F25	15	5	++	++	200	7 months
1800	M25	4	1	+	+	400	2 months
1170	M25	long	3	++	++	300	3 months
712	M30	16	8	++	++	2-300	not
1673	F30	3	2	++	++	400	not
1590	M40	5	2	++	++	300	6 months

series of patients with advanced lepromatous leprosy, who were prone to repeated, severe reactions prior to the trial, all but one being steroid dependent (Table 1). The duration of clofazimine treatment was up to 5 years.

Dosage of Clofazimine

In 7 patients treatment was started with 300 mg clofazimine daily; in the others with 100 mg daily, followed mostly by a weekly increase with 100 mg daily, to 300 mg daily, or in a few patients to 400 mg daily, and in one patient to 600 mg daily. One patient was given only 200 mg daily. The drug was given in divided doses, in order to promote resorption of the drug. Treatment was continued as long as accepted by the patient or until smears had become negative. The drug was reduced to 100 mg daily when reactions had subsided or had become mild.

Assessment

Skin smears were taken at 2 monthly intervals, each time at 5 sites. They were examined locally by the same technician. Skin biopsies were taken at 4-6 months

Reactions after clofazimine	Abdominal pain	Discontinuation of clofazimine	Other complications
occasional, mild	+	temp. 3 months	
none	–	not	
less frequent, less severe	±	temp. 1 month	dysentery
rare, mild	+	temp. 7 months temp. 3 months stop after 46 months	
1 year frequent, moderate thereafter rare, mild	–	–	
occasional, mild	–	–	
single only	–	–	diabetes † apoplexy
less frequent, less severe	+	temp. 1 month stop after 55 months	† pneumonia
occasional, slight	–	–	
period of neuritis, 4 months *temp.* steroids	+	stop after 46 months	† nephrotic syndrome
mild, after 1 year none	+	stop after 34 months	
temp. steroids 7 months	+	stop after 32 months	
slight to moderate	–	–	
one serious, thereafter none	+	stop after 31 months	† nephrotic syndrome
less frequent, less severe	–	–	† unspec. infection
severe, frequent	+	stop after 19 months	
none	+	temp. twice 2 months	† resp. infection

TABLE 2

Infiltration Index biopsies (% infiltration in section)

Months	0	4	10	14	18	22	26	30	34	39	44	52	57
1212	20	20	25	40	20	5	5	10	5	5	5	2	2
970	10	15	5	10	2	5	15	5	5	5	2	2	2
1455	15	30	30	15	5	10	10	10	5	2	10	10	10
1228	10	20	10	20	5	2	10	5	5	5	2	2	2
220	25	15	10	10	5	5	5	5	10	10	2	2	2
914	70	30	10	5	5	5	2	5	2	20	2	2	†
1202	40	15	15	20	25	30	30	25	30	30	20	†	
349	20	50	40	50	25	20	20	80	25	40	30		
281	15	35	25	10	15	25	15	5	25	10	10	2	5
1000	20	60	80	20	15	25	40	20	15	25	20	15	2
555	10	40	20	15	20	20	15	30	15	5	5	†	
1519	30	10	10	5	20	5	10	10	5	2			
1800	15	10	5	10	5	10	5	5	5	2			
1170	30	10	10	20	25	2	5	2	5	5	†		
Average	24	26	21	18	14	12	13	16	11	12			

intervals, when possible each time from the same lesion. They were processed and examined in Amsterdam. The Bacterial and Morphological Indices were assessed blindly.

Clinical Results

Clinically all patients responded rapidly to the drug with reduced infiltration of the skin and puffiness of the face. After the initial favourable response the clinical improvement became more gradual and slow. The reduction of the visible infiltration in general corresponded with the decrease in infiltration index (Table 2).

Bacteriological Results

Because all patients had previously received treatment, intact bacilli were rarely found. The majority of the bacilli were granular at the onset of the trial. In most patients the BI decreased gradually in smears (Table 3) and in biopsies (Table 4), but on the average the decrease was relatively slow. In a few patients no significant decrease was found.

The average BI in smears at onset was 2.0 and in biopsies 4.5. After 2½ years the average BI had decreased in 1.3 and 3.0 respectively, corresponding with an average annual decrease of 14% and 13% respectively. During the trial 6 out of 17 patients became bacteriologically negative in smears and biopsies.

Effect on Reactions

In most patients ENL reactions occurred, frequently accompanied by neuritis, arthralgia, tibial pains (periostitis, osteitis), swelling of hands and feet or, rarely by orchitis. In a few patients, ENL being absent or very mild, the latter symptoms were predominant. They were counted as reactions.

After the introduction of clofazimine fresh reactions were seen in most patients. Only after several months of treatment did the reactions become less frequent and severe, indicating a lag phase in the suppression of reactions. In 8 patients the reactions subsided completely after 2-13 months of treatment, with an average of 7 months. Four of these patients had transient relapses of reactional phases, 2 after fading out of steroid therapy, one after an interruption of specific treatment and reintroduction of clofazimine and one after replacement of clofazimine by DDS. In one patient, after 2 months of treatment, the reactions improved from severe to mild and became infrequent, but only after 33 months did they subside completely. Another patient became free of reactions only after 54 months, when smears had become negative. In another patient mild, occasional reactions continued until 1 year after smears had become negative.

One patient continued with very mild reactions for 4 years, after which he left the trial. Five patients never became completely free of reactions during the trial, although the reactions became less frequent and severe. Fourteen patients were completely steroid dependent. In 11 patients, after an average period of 10 months, steroid treatment could be discontinued. In 2 patients the dosage of prednisolone could be reduced, but low steroid dosages were needed throughout the trial. In 1 patient a dosage of 30 mg prednisolone daily had to be maintained. In 2 patients, after weaning off steroids, prednisolone treatment had to be resumed temporarily for periods of 5 and 8 months respectively.

TABLE 3

Bacterial Index in smears

Months	0	4	7	11	14	18	22	26	30	33	39	43	46	50	54	57	61
1212	3.2	2.2	1.6	1.4	1.4	1.4	1.2	1.0	0.8	0.8	1.2	0.8	1.4	0.4	0	0	0
970	1.4	0.8	0.6	0.8	1.0	0.6	0.8	0.4	1.0	0.6	0.8	0.8	0.4	0.8	0	0	0
1455	1.8	1.6	1.6	1.4	1.6	1.8	1.6	1.0	1.2	1.6	1.0	0.6	0.8	0.4	0	0	0
1228	2.2	1.0	0.8	1.0	0.8	1.0	0.8	0.6	0.8	0.4	1.0	0.8	0.4	0.8	0	0	0
220	2.0	(1.8)	1.6	1.2	1.0	1.6	1.0	0.8	0.6	0.4	1.0	1.0	0.6	0	0	0	0
914	1.4	2.0	1.6	2.0	1.8	1.8	1.6	1.8	1.4	1.8	2.0	1.6	0.8	0.6			
1202	1.2	(1.2)	1.2	1.2	1.0	1.6	1.0	0.6	1.0	0.8	1.0	0.8	1.4	0.8	†		
349	2.4	2.6	3.0	2.4	2.8	2.6	2.4	2.4	3.0	1.6	1.4	2.0	†				
281	2.2	1.8	1.8	1.8	2.0	2.2	1.8	1.6	2.2	1.6	1.6	1.8	1.8	1.0	0	0	0
1000	1.6	2.4	1.8	1.6	2.6	2.6	1.8	2.4	2.8	2.8	1.2	1.4	1.2	1.0	0	0.2	0
555	3.2	2.2	1.8	2.0	2.4	(2.1)	1.8	2.2	1.8	1.6	1.2	2.4	1.4	1.2	†		
1519	1.1	1.0	1.2	1.2	1.0	1.0	0.6	0.8	0.4	1.0	0.4						
1800	2.6	(2.4)	2.0	2.0	1.8	1.6	1.6	1.6	1.0	2.2	1.0	1.2	0				
1170	1.0	1.4	1.0	0.6	0.6	0.6	0.6	(0.6)	0.6	0	0	†					
Average	2.0	1.8	1.5	1.5	1.6	1.6	1.3	1.3	1.3	1.2	1.1						
712	3.6	3.0	3.4	2.8	2.8	0.6	†										
1673	2.0	2.0	2.0	3.3	1.8	1.4	1.8	1.2	1.4	0.2	0.6	0.6					
1590	2.4	2.8	3.6	3.2	†												

TABLE 4

Bacterial Index in biopsies

Months	0	4	10	14	18	22	26	30	34	39	44	52	57
1212	3.5	4.0	5.0	5.0	6.0	4.0	4.0	2.0	3.0	3.0	1.0	0.5	0
970	4.0	2.0	3.0	2.0	3.0	3.0	3.0	4.0	3.0	3.0	3.0	0.5	0
1455	6.0	3.0	3.5	3.0	3.0	3.0	2.0	1.0	1.0	0	0	0	0
1228	2.0	3.5	4.0	2.0	3.0	3.0	1.0	3.0	3.0	2.0	0	0	0
220	3.5	3.0	4.0	3.0	3.0	3.0	4.0	3.0	3.0	1.0	0	0	0
914	4.0	4.0	4.5	4.0	4.0	4.0	4.0	4.0	4.0	3.0	2.0	1.0	
1202	3.5	5.0	4.0	4.0	4.0	1.0	1.0	3.0	2.0	1.0	1.0	†	
349	6.0	6.0	6.0	5.0	4.5	4.0	2.0	4.0	4.0	3.0	†		
281	6.0	6.0	6.0	6.0	4.0	5.0	4.0	4.0	3.0	3.0	0	0	0
1000	6.0	6.0	6.0	6.0	6.0	6.0	5.0	6.0	4.0	4.0	3.0	1.0	0
555	6.0	6.0	6.0	6.0	6.0	4.0	4.0	5.0	5.0	3.0	3.0	†	
1519	4.0	4.0	3.0	3.0	3.0	2.0	2.0	3.0	4.0	1.0			
1800	5.0	4.0	4.0	4.0	3.0	4.0	4.0	0	0	0			
1170	4.0	4.0	1.5	1.0	1.0	1.0	1.0	0	0	0	†		
Average	4.5	4.3	4.3	3.9	3.8	3.4	2.9	3.0	2.9	1.9			

Other Complications

In this trial a high percentage of the patients, 10 out of 17, developed more or less severe abdominal pain. In 3 patients the complaints were moderately severe, requiring temporary interruption of clofazimine treatment for periods of 1-3 months. In 7 patients the complaints were severe and persistent and clofazimine treatment had to be discontinued ultimately, after an average period of treatment of 38 months. In most patients the pain was located in the stomach region, but in 2 patients an enteritis with the clinical picture of dysentery was seen.

The outcome of fractional tests of the stomach contents was not consistent. Hyperacidity as well as hypoacidity and normal acidity were found. In 2 patients barium contrast X-ray screening revealed a large, hypotonic stomach with gross gastritis.

The stomach complaints subsided in most patients soon after withdrawal of clofazimine, but in 1 patient they persisted after discontinuation of the drug. During the trial it was found that 1 patient suffered from a latent diabetes, which later became manifest. This patient died of apoplexy. In 3 patients albuminuria was found. The patients had very advanced disease of long duration, with a long history of reactions. Two of these patients died after a nephrosis syndrome.

Three other patients died after secondary infections, pneumonia, descending upper respiratory tract infection and an unidentified infection respectively.

Two patients were pregnant and delivered during the trial. One child died after 3 hours. The cause of death could not be clarified. The mother of this child was steroid dependent, but 4 weeks before delivery prednisolone was discontinued. The second child was healthy.

Discussion

In 14 patients who completed 2½ years of treatment with clofazimine the BI in smears decreased from an average of 2.0-to 1.3 and in biopsies from 4.5 to 3.0, corresponding with an average annual decrease of 13% and 14% resp. This is somewhat slower as compared with patients on sulfone treatment (on the average about 17%). Of the 6 patients who completed 5 years of treatment 5 became negative, one after 4 years and 4 after 4½ years of treatment. On the other hand in some patients the bacteriological response to clofazimine was decidedly slow and unsatisfactory. Resistance to clofazimine is unlikely because the patients had not received clofazimine prior to the trial and the response to clofazimine was already disappointing in the first years of the trial. Resistance to clofazimine has not yet been reported.

No correlation was found between a slow bacteriological response and a long period needed for weaning of steroids (>6 months), not with stomach complaints. The decrease in BI was somewhat slower in patients with a very long duration of the disease (>10 years) and with a long duration of previous treatment ($\geqslant 5$ years).

In the first months of treatment, in spite of dosages of 3-400 mg clofazimine daily, several patients continued with moderate to severe reactions. The lag phase in the effect of clofazimine suggests that it is dependant on the building up of a deposit of the drug in the tissues. Several other patients continued with mild reactions throughout the trial. One patient continued to suffer from frequent and severe reactions, in spite of 400 mg clofazimine daily. One patient remained steroid dependent. The overall results of this trial, with respect to the suppression

of reactions by clofazimine, are somewhat less favourable than those that have been reported from other trials and they are not significantly better than those that have been reported from trials with 100 mg clofazimine daily. No correlation was found between the effect of clofazimine on the reactions and the duration of the disease or the bacteriological response to treatment. No explanation for the less favourable effect of clofazimine in some patients was found.

Mild to moderate gastro-intestinal complaints have been reported from other trials. In this trial a very high incidence of abdominal pain was found. In several patients the complaints were severe, with excessive pain and vomiting after each medication. Some patients refused to take the drug again after temporary discontinuation, for fear that the pain might recur.

In a few patients, after conventional treatment of gastritis or after treatment of latent amebiasis or, if a secondary intestinal bacterial infection was suspected, after treatment with sulphonamides, it was possible to reintroduce clofazimine, with a better tolerance. In 7 patients clofazimine had to be withdrawn completely. No correlation was found with long duration of disease (5 out of 9 patients with a history of >10 years) or with long previous treatment (3 out of 6 patients with $\geqslant 5$ years treatment) or with steroid dependance (9 out of 14 steroid dependent patients) or with the time needed for withdrawal of steroids (7 out of 10 patients who continued with steroids for $\geqslant 6$ months). Also no correlation was found with sex (8 out of 12 males and 2 out of 5 females). In the majority of other trials lower dosages of clofazimine have been used or the higher dosages have been administered for shorter periods, and the duration of the clofazimine treatment has been shorter. In some of the patients in this trial the complaints subsided after reduction of the dosage. This suggests that the complaints are to some extent dose related.

In several of the patients a history of severe enteritis or dysentery was found in the records. This suggests that clofazimine acts as an irritant in particular if the intestines have already become irritable by other factors. Though the present trial confirms that many patients greatly benefit from clofazimine treatment, it also shows that for some patients it is not the final answer to their problems.

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Some Clinical and Laboratory Signs Indicating External Compression of a Nerve Trunk in Leprosy: Details and Rationale

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The details and rationale of clinical signs which when positive indicate the presence of active external compressive and traumatic factors affecting an inflammed nerve trunk in leprosy are described. A new laboratory test suggesting peripheral vascular insufficiency and indicating the need of posterior tibial decompression is also described. The increasing trend towards nerve surgery in leprosy is reviewed and the need for proper selection of cases is stressed.

Neuritis and nerve damage in leprosy, in its etiopathology, has two essential components, the effects of the bacillary infection (including immune mechanisms) and the effects of local traumatizing factors on the affected nerve. The latter can be prevented, or their effects ameliorated, by surgery. When a nerve passes through a rigid tunnel this situation predisposes to mechanical compression and trauma, especially subsequent to nerve enlargement. The situation is worsened when nerve inflammation and oedema supervene. As most of these tunnels are on the level of a joint, the joint movements provide further trauma to such a nerve. The sites of nerve involvement in leprosy seem to be restricted to such vulnerable positions. This communication presents the details and rationale of some clinical and laboratory tests which indicate the active presence of such compressive and traumatic factors. These tests when positive are an indication in the opinion of the author, that nerve surgery is likely to be beneficial in these cases, especially when these signs persist in spite of medical treatment including a short course of prednisolone.

Ulnar Nerve

THE STRETCH SIGN

The sign is positive when there is pain in the ulnar nerve behind the elbow on flexion of the elbow. Depending on the severity, 3 grades are recognized;

(i) The ulnar nerve pain is elicited only when the elbow is flexed passively just beyond its full active range.

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(ii) There is pain in the ulnar nerve on active flexion of the elbow but without any flexion restriction;

(iii) There is flexion restriction of the elbow, usually beyond 100°, because of the pain in the ulnar nerve.

Rationale—normally the increase in length of the extensor surface of the upper limb during elbow flexion is compensated by medial movement of the ulnar nerve in its tunnel behind the elbow. This is similar to the compensatory movement volarwards of the lateral bands of the extensor expansion at the proximal interphalangeal joint level during finger flexion. This essential excursion of the nerve is restricted when the nerve is thickened. Further elbow flexion now results in lengthening of the nerve. As a nerve cannot really be stretched or elongated, this results in trauma to the nerve which is expressed by pain in the nerve on elbow flexion. Hence the term "The Stretch Sign". This sign was first described by Marneffe in 1928 as mentioned by Prof. Diez (1942).

THE TUNNEL COMPRESSION SIGN

When the patient is asked to contract the flexor carpi ulnaris and flexor superficialis against resistance, (flexion and ulnar deviation of the wrist with the fingers fully flexed), he complains of pain in the ulnar nerve behind the elbow.

Rationale—the roof of the ulnar tunnel behind the elbow is formed by the aponeurosis of origin of the flexor carpi ulnaris from the medial epicondyle and the olecranon. The upper arching fibres of the flexor superficialis also take part in the formation of this roof. The upper one inch or so of the flexor carpi ulnaris muscle through which the ulnar nerve passes below the elbow also can compress the nerve. Contraction of these muscles can cause compression of an already inflamed and oedematous ulnar nerve in leprosy, thereby producing pain.

PAINFUL DISLOCATING NERVE

When this sign is positive, on flexion of the elbow the ulnar nerve dislocates and in complete flexion lies anteromedial to the epicondyle and the patient complains of pain.

Rationale—in 5% of normal individuals, a dislocating ulnar nerve can be observed, (WHO report, 1960). However, when the ulnar nerve is enlarged and inflamed, this friction-trauma during dislocation causes additional injury and hence the pain.

Lateral Popliteal Nerve

STRETCH SIGN

Restriction of knee extension because of pain in the lateral popliteal nerve in its upper course constitutes the sign. The rationale is similar to that of stretch sign in the ulnar nerve. Usually when the sign is present the lateral popliteal nerve is found to be very markedly thickened and tender.

Posterior Tibial Nerve

THE RETROMALLEOLAR SIGN

This is elicited by noticing that the retromalleolar space (behind the medial malleolus) which is normally concave becomes filled up or may even become convex, the swelling being nonfluctuant.

Rationale—the thickened, inflamed posterior tibial nerve secondarily compresses the posterior tibial vessels and there is associated venous and lymphatic stasis due to tunnel compression. The vascular changes are well documented by Carayon (1971).

LABORATORY TESTS

A higher total leucocyte count in the toes as compared to that in the peripheral venous blood: the test is considered positive when the total leucocyte count, is considerably higher in the toes than in the venous blood. A difference of at least more than 500 per mm^3 is considered significant.

Rationale—we have been doing this test since 1972 after coming across the work of Czaczkes and Drefuss (1957) who have shown such increase in the leucocyte count in the peripheral blood in conditions of peripheral vascular insufficiencies. They found this to be true in cases of Reynaud's disease, ergot and phosphorous poisonings, frost bite and similar conditions characterized by peripheral vascular insufficiency. We have found that in cases of posterior tibial neuritis similar findings are obtained. For example in 22 cases which had posterior tibial neuro-vascular decompression; either for posterior tibial neuritis alone or together with an intractable planter ulcer, in our hospital during 1974, the findings were:

1. A higher leucocyte count in the toes was noted in all. The difference between the total leucocyte count in the toes and in the peripheral venous blood was more than 1000 per mm^3 in 9 cases, 700-1000 in 3 cases, 500-700 in 3 cases and less than 500 in 6 cases, no data in one case.
2. In 18 of these the investigation was repeated post-operatively and the findings were: in 8 cases, the difference in the 2 counts was less than 500; in another 8 cases, the difference was more than 500. In 4 of these patients even though the toe count was higher than that in the peripheral venous blood, the difference was less than pre-operatively; in 2 cases, the count in the toes was higher than the pre-operative figure. In all these cases with higher than 500 per mm^3 leucocyte count in the toes pre-operatively, at operation marked compression of the neurovascular bundle was noted. The operation findings in such cases were described in detail by the author (1973; 1975).

A higher count in the toes we take as an indication of distal peripheral vascular insufficiency. Carayon (personal communication) has found a higher red cell count in the toes in similar cases and according to him that indicates a congestive condition in the foot because of autonomic (sympathetic) disturbance caused by compression or damage to the posterior tibial nerve. The insufficiency of blood supply to the foot in these cases is caused by compression of the posterior tibial artery in the retromalleolar tunnel secondary to increase in the contents of the tunnel caused by the enlarged posterior tibial nerve. Often, as seen during the decompression operation, the artery has a tortuous course, and it often bends at the level of the medial malleolus and lies between the bone and the nerve, in which situation, it is more likely to be compressed. As pointed out by Carayon (1964) there is often hypersympathetic activity secondary to neurovascular compression associated not only with peripheral vasoconstriction but also with opening out of shunts which further diminish the distal blood flow. Peripheral venous stasis also probably occurs if the often seen engorgement of the veins accompanying the posterior tibial artery is considered. Local oedema (around ankle) is also frequently seen. This also provides the rationale of periarterial sympathectomy.

Discussion

There is an increasing interest in nerve surgery in leprosy as evinced by the number of papers published on the subject from different centres in the last decade. The physiopathological basis corroborated by clinical and contrast radiographic findings (neuro-lymphangio and angio-graphies) has been well propounded by Carayon (1971) and others. At the Xth International Leprosy Congress in Bergan, in the words of S. G. Browne (1973) "A very fruitful discussion took place on the matter of operating on the acutely inflamed peripheral nerve". Among the various published works, Callaway *et al.* (1964), Vaidyanathan and Vaidyanathan (1968), Parikh *et al.* (1968), Gabel (1973) and Palande (1973), report varying grades of clinical recovery by surgery (in rather unselected cases) in more than 50% of nerves. Carayon (1973) while presenting his results of direct nerve trunk surgery on 568 nerves at the Bergan International Conference reported clinical recovery in 79% of cases operated within 3 months and in 65% when operated within the first 6 months. Carayon further stressed the need of proper selections of cases. Enna and Jacobson (1974) while reviewing all neurolysis cases done in Carville in 12 years, report: "we believe that overall the surgery was beneficial in terms of lessening the problem of chronic neuritic pain and preventing further paralysis and deformity". Antia (1974) also agrees that "careful and complete release of the thickened nerve may not only relieve the pain, but may also result in recovery of sensory and motor function". He further points out that inadequate appreciation of the existing pathology and of the physical factors responsible for nerve damage is probably the main reason for the conflicting reports and views; to which can be added, an inadequate appreciation of the limitations of surgery. The above stresses the need of proper case selection as also the necessity to curb over-enthusiasm either for, or against, nerve surgery. The significance of the higher leucocyte count in the toes as described is open to question because of the number of factors–physiological, technical and others–influencing the results of this investigation. However, it can definitely be used as an aid to decide if surgical decompression of the posterior neurovascular bundle is required or not. The other clinical signs described definitely imply the presence of an external compressing factor the release of which is very likely to benefit the patient and aid in nerve recovery.

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Rehabilitation by Amputation

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A retrospective study of lower limb amputations in leprosy patients at ALERT is reported. Charts were reviewed and patients were interviewed. Surprisingly, there was very high patient acceptance of both the amputation and of even rather mediocre prosthesis. In addition almost all patients became independent and self-supporting by a culturally acceptable means. Prior to amputation most had been totally dependent. It is therefore concluded that amputation is acceptable rehabilitative surgery for those whose feet have become so mutilated as to prevent full weight bearing.

For many years two dicta have ruled surgeons contemplating amputation; first, any leg is better than no leg; second, the longest stump is the best stump. These were "the law and the prophets", and all that remained was but commentary.

In developing countries these laws have been clung to with fervour. Where excellent prosthetic service was not available, amputation was held to be anathema. Cochrane's text (1964) does not even discuss criteria for amputation. More recently Fritschi (1971) regards amputation as the last and least desirable therapy. After all attempts at sequestrectomy, grafting, tendon transference, arthrodesis, casts, and cumbersome and ugly footwear and orthoses have failed, then with reluctance amputation is accepted. He says, "No surgeon is justified in removing a limb unless he can provide one which is an improvement".

In an attempt to evaluate these attitudes objectively a retrospective study was done. An attempt was made to find, examine, and question all amputees attending the ALERT clinics. A monthly prosthetic review clinic was established, facilitating not only the study but preventive and curative maintenance of prosthesis as well. At the beginning of the study half the patients had stump ulcers. At the penultimate clinic with 24 attending, only 2 had ulcers and one of these had a new prosthesis.

Sixty-eight cases with 81 amputations were reviewed. Fifty-eight persons with 71 amputations (12 bilateral) were interviewed. Ten persons had died or could not be traced, and only their charts were reviewed.

Fifty-seven patients were men. Eleven were women. Ten men and 3 women had bilateral amputations. There was a significant tendency for these patients to be more aggressive and harder workers than their fellows. This may account for their more frequent and chronic injuries.

The average age at time of amputation was about 35 in both men and women

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following an average period of 6 years of what the patient considered to be total disability. Six amputations were done for epithelioma of the foot. (Of these 4 died of metasteses in less than 5 years. Two are living and apparently well after 2 years.) The remaining amputations were done for combined mutilations of bone and soft tissue.

Levels of amputations were as follows:

Mid foot	4
Pirogoff's	12 (6 were un-united)
Syme's	18
Below knee (mid-leg)	43
Through knee	2
Above knee	2

In the case of both Pirogoff's and Syme's amputations there was a marked tendency for posterior displacement of the heel pad if the Achilles tendon had been left intact.

An attempt was made to map stump sensation. No meaningful pattern was found except that there was more sensation on the sides than on the end of most stumps. Therefore it can be concluded that a prosthesis distributing weight around the sides of the leg is safer than one using end bearing technique.

Almost all stump ulcers were due to ill-fitting sockets. The large majority healed after revision or replacement of the old socket. As expected there was direct correlation between the absence of sensation and persistent stump wound and vice versa.

The mobility of patients was very difficult to assess, and could only be determined approximately by asking the patient where he walked to his work and how many times per week. The average distance estimated per day was 4 km, with a range from 200 m to 18 km. All of the group except 6 were using either a pair of crutches or walking sticks for additional balance or support.

Associated hand deformities were very significant:
8 had normal hands (WHO grade 0)
4 had areas of anesthesia (WHO grade 1)
14 had anesthesia with intrinsic paralysis (WHO grade 2)
26 had mutilated hands (WHO grade 3)
(Unfortunately, this aspect of the problem was not considered during initiation of the study, and so only 52 of the interviewees provided the data.)

The most dramatic aspect of this study was in the area of patients' satisfaction and rehabilitation. One man who had had chronic ulcers was discontented with his amputation. One who had ulcers, but whose below knee amputations were done by a train was also discontented. Of the remaining 56, all felt that amputation had been of real benefit to them.

All except 6 were content with their prosthesis. About half of those who were content to wear simple elephant boots desired a normal-looking shoe for cosmetic reasons.

The patients' attitudes varied from stoic acceptance of amputation as a necessary phase of their treatment to frank appreciation. One man, now a landlord, with Syme's amputation for 35 years, had used an inverted cowhorn as a prosthesis for 25 years (Fig. 6). He now has a cosmetic resin and plastazote

shoe (Fig. 7(a)). His testimony was, "When the amputation was first done, I realized that it was necessary to save my life. Nevertheless, I was very angry with the doctor, my friends and all people. Since then I see my friends who had ulcers then, still hobbling about on their ulcers. Whereas, I with the help of God and a stick, go where I wish and do what I wish."

Of all the 58 persons interviewed only 5 were not self supporting. Two of these had been inpatients in other institutions for years.

3 persons were inmates of the Government Reception Centre for vagrants.
12 persons were employed in crafts and daily labour.
12 persons were self-employed in petty trade or were property owners with houses which they were giving for rent.
25 persons were self-employed as beggars.*

Of the beggars only 1 became a beggar because of the amputation, and this was a woman who stated that she had been divorced, not because of her leprosy, but because of the amputation. All had been completely disabled for an average of 6 years with a variation from 1 month to 30 years. All save 7 had mutilated hands. Because they had to travel by bus or walking 15 km a day to beg it would seem that restoring the ability to walk with a prosthesis freed them from total dependence. The fact that of 25 beggars 17 had mutilated hands and 5 more had contracted claw hands would indicate that perhaps the hand deformity was more contributory to their choice of profession than was the amputation.

Indications for Amputation

(Figs 2-5)

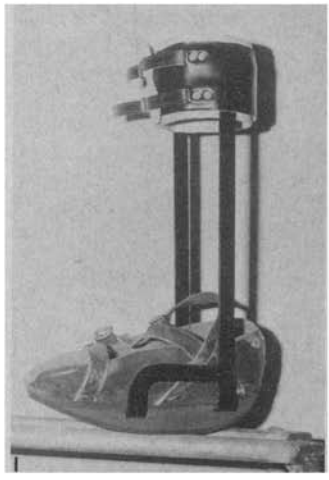
These may be summarized as any limb which has a destruction of its weight-bearing surface and bony architecture to the extent that no reconstructive operative procedure can be performed. In the forefoot, ulceration is often associated with long-standing equinus deformity. It is usually possible to perform a tendon transfer, or if the foot is shortened, ankle fusion in the correct position. A good heel pad and at least half the weight bearing area of the foot is necessary for this latter procedure. A fixed ankle brace (Wollstein, 1972) is usually required (Fig. 1).

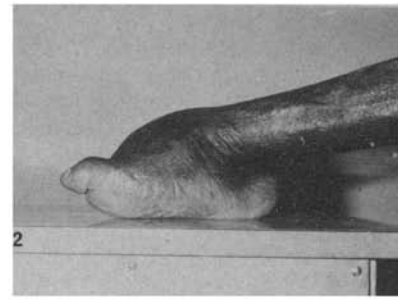
Tarsal disintegration may result in an inverted foot. This can usually be corrected by sub-talar arthrodisis, provided a stable forefoot is present, and an adequate area of scar-free weight-bearing plantar skin is available (Fritschi, 1971).

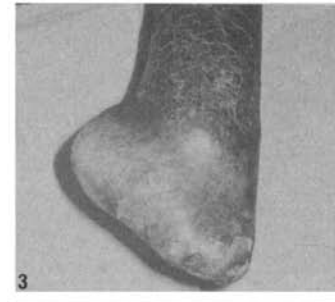
Tarsal disintegration can also result in a mid-tarsal disorganization with resulting rocker bottom foot. This condition is rarely amenable to reconstruction. Similarly, a heavily scarred heel, especially if this is associated with an unstable forefoot, will usually require amputation. Calcaneal disintegration with Achilles migration prevents use of the forefoot.

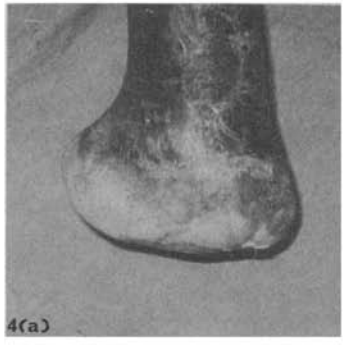
When in any doubt a trial should first be made with a fixed ankle brace (FAB walker) with rocker sole. If this does not maintain the foot ulcer free, then an amputation is indicated.

* We fully justify this as a self employment on several bases: It is hard labour, requiring several kilometres of travel daily. It requires initiative and perseverance. In the Orthodox Christian and Muslim communities, the giving of alms is a godly act—even a means of grace, and the receiver of alms is therefore a necessary member of society in Ethiopia.









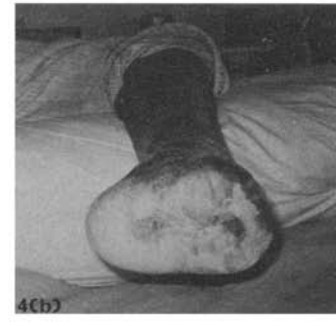


Fig. 1. The FAB walker incorporates a moulded plastazote insole on a microcellular rubber foundation with a rigid sole, a fixed ankle and a rocker bottom. This eliminates all foot and ankle flexion transmitting motion to the shoe contact surface. Force is still transmitted from the tibia through the ankle joint, and so some bony continuity is required.

Fig. 2. This foot has undergone Charcot degeneration. Skin and fat are intact. The x-ray demonstrates that the weight distributing arch-truss of the foot is entirely destroyed. Further weight bearing will lead inevitably to penetration of the sole by the tibia. A Syme amputation will preserve the heel pad.

Fig. 3. Although a talectomy and calcaneo-tibial compression fusion could make this foot plantigrade it would still have less than half the weight bearing skin. Add to that the severe scarring of the tip and the balance is in favour of Syme amputation.

Fig. 4. This foot is in equinus although the loss of the forefoot masks that fact. The plantar surface is almost wholly scar tissue. The heel pad has been preserved due to the equinus and can be brought around into functional position by a Syme amputation.

Not infrequently gangrene due to infection will demand amputation. Epithelioma occurring in chronic ulcers is not rare and demands amputation to save life. It must be confirmed by biopsy as the clinical appearance can be deceptive.

Amputations through the midfoot frequently occur spontaneously due to loss of toes and metatarsal heads. A filled shoe then makes a moderately acceptable prosthesis, but foot end ulceration, especially if there is a fixed equinus deformity, may persist unless a rigid rocker sole is applied to the shoe.

The various modifications of the Pirogoff amputation, which attempts to fuse a retained portion of the calcaneus to the tibia, fail to arthrodese in many cases. They then become dislocated backwards by the active calf muscle through the intact Achilles tendon.

Only 2 types of amputation are therefore recommended: The Syme amputation, and the below knee, where the stump is about 14-17 cm long with a myofascial flap to cover the tibial end.

The Syme amputation should include excision of the malleollae and the cartilage of the tibial mortice. The Achilles tendon should be excised to prevent subsequent posterior dislocation of the flap. We make a slight fish-mouth incision at the ankle joint, saw the tibia and fibula 1 or 2 cm above the joint, and dissect from above downward sub-periosteally. This is less traumatic to the tissues and leaves a less bulbous and more stable pad than the classical Syme (Fritschi, 1971).

There is adequate and extensive literature on below-knee amputations in standard surgical texts. The length of 14-17 cm is suggested because it makes prosthesis fitting and leverage much better. The myofascial flap is needed to protect the skin from the tibial end. Especially in situations where the prosthesis is not perfect, there is a tendency to end bearing which is made safer by the thicker pad.

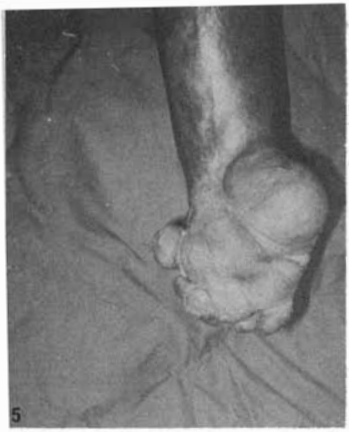
Prostheses

(Fig. 6-10)

For Syme's amputation acceptable leather "elephant boots" (Fig. 7) can be made by a village shoemaker. The most appropriate Symes' prosthesis seems to be a moulded long socket, bearing weight not only on the end, but on the upper tibial flare, and on the patellar tendon as well. This may require a window for donning the prosthesis if the heel pad is bulbous. If facilities are adequate a rocker foot should be provided for cosmetic reasons. This is a frequent request from the patient with an "elephant boot".

For below-knee amputations a bent knee prosthesis with simple pylon can be made by a competent cabinet maker or wood carver (Fig. 8). We have not found that this leads to knee contracture. Nor does it hinder later patellar tendon bearing prosthesis fitting. It should be used in centres not having a regular limb shop.

At the next level of technical sophistication is the Pfaltzgraff prosthesis (a plastazote socket with resin leg moulded directly to the stump) requiring somewhat more skill and special materials than the bent knee prosthesis (Pfaltzgraff, 1963) (Fig. 9). It is technically within the scope of any group making special shoes and sandals for deformed feet. However, we find that without relining about every 3 months, the plastazote liner tends to flatten. The socket is thereby enlarged and becomes end bearing rather than patellar tendon bearing.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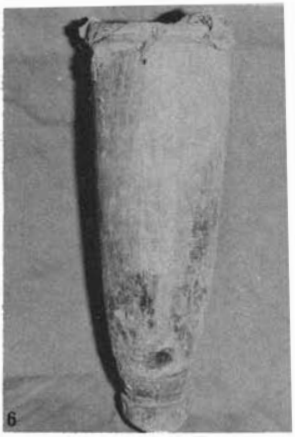
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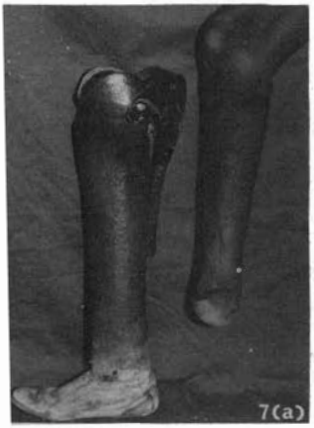
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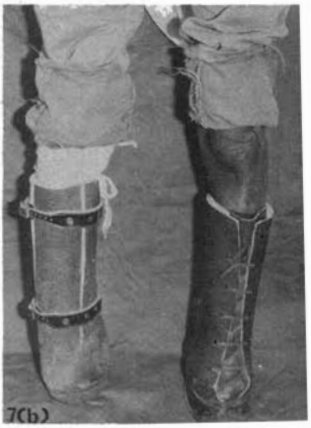
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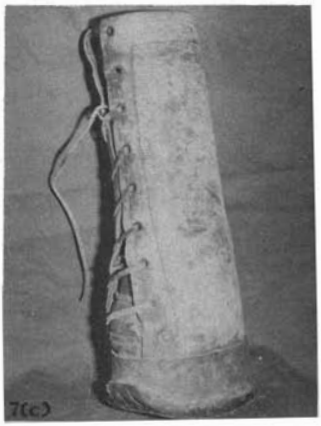
7(c)

Consequently, pistoning of the stump, callosities and ham string ulcerations occur.

The hard socket patellar tendon bearing is by far the best prosthesis if it fits perfectly. It is technically difficult to make, but any skilled craftsman can learn this task, though it does require special training, tools and materials. Many leprosy treatment centres are able to produce such limbs. Others should seek opportunity to send a craftsman for this training.

In our situation, we think that the best foot is the SACH–rocker (Fig. 10). This is a solid ankle, cushioned heel with a rocker bottomed polymerized resin foot unitary with the leg. This has a slightly odd appearance, but gives a very good gait. The rubber forefoot of the usual Western SACH foot tends to break after about 6 months use and is thus too expensive for services with restricted resources.

Discussion

In the past when chronically ill patients were isolated from society because of their disease; when leprosaria consisted a series of low cost huts; when a patient's time was not a considered commodity, and when the patient could not expect re-integration into a society that rejected him; at that time spending months and even years in a futile attempt to save a doomed foot was perhaps justified.

Today, each person's time must be considered his valuable possession. Soaring hospital costs also must realistically be counted. In our series the average time of total disability was 6 years. During much of that time, the patients were hospitalized and/or consuming expensive materials such as bandages, antibiotics, plaster of paris and professional staff hours. The expenditure of such commodities is surely worthwhile if the natural foot can be restored to prolonged and useful service.

Our patients obvious contentment, their assumption of a place in their own society, and their increased mobility, encourage us to believe that amputation is not just mutilation but is indeed rehabilitation.

Fig. 5. There remains here an adequate area of well preserved plantar skin and fat. The bony architecture has been entirely scrambled due to osteo myelitis, Sequestration and Charcot phenomenon. Scarring has embarrassed blood supply and elephantiasis has made the skin about the ankle very fragile. Therefore a BK amputation is probably the wisest choice.

Fig. 6. This inverted cow's horn, padded with rags, served as a prosthesis for a Syme's amputation for 25 years.

Fig. 7. Several types of prosthesis for Syme's and Pirogoff's amputations. (a) A weight sharing prosthesis moulded to accept part of the weight on the heel pad and part on the tibial condyles and patellar tendon. This requires a distal end smaller than that obtained with the classical Syme's retention of moleolae (see text). (b) A resin and stockinette "Elephant Boot" with plastazote liner and window for donning. This fits a Pirogoff's amputation stump with its large distal end. (c) A simple leather and auto tyre "Elephant Boot" which can effectively have a plastazote liner. All of the above models have microcellular rubber pads for the weight-bearing stump end. Patients such as farmers who walk on very uneven surfaces prefer the elephant boot to the prosthesis with a foot.

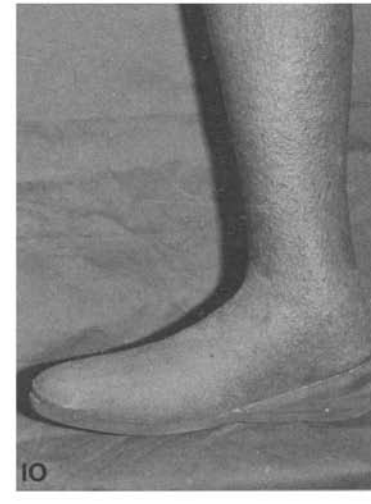

Fig. 8. The bent knee prosthesis gives a stiff-legged gait but is simple to make and very cheap. Patients find it quite satisfactory. One patient whose prosthesis was made with a one-inch soft iron rod for a leg piece wore it down 6 cm in 2 years. He came back only because his limb was too short.

Fig. 9. The Phaltzgraff prosthesis pictured with its plastazote liner removed is mid-way in sophistication and cost between the bent knee prosthesis and the hard socket patellar tendon bearing prosthesis. Some special skills and materials are needed, but any competent shoemaker can learn the techniques in a week or two.

Fig. 10. Because with rough usage the standard SACH foot and rubber toe do not last long an integral resin foot is preferable. Ideally the rocker conformation should be more accentuated than the model pictured.

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Below Knee Amputation

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In the management of severely damaged feet in leprosy patients amputations still play an important role. Probabilities are high that they will continue to do so for many years to come. Most leprosy patients who need that kind of surgery come under the care of medical officers with little or no training in sophisticated orthopaedic surgery. Unfortunately the traditional techniques for below knee amputation are fairly difficult to perform adequately. A less than perfect result makes it difficult to fit a prosthesis. The high risk of complications with traditional techniques, and the scarcity of prosthetic services, constitute a real need for a simple operation with a high percentage of good results.

Recently a new method has been advocated. It aims at simplifying the surgical technique, at avoiding the grave risk of ischaemic necrosis of the anterior skin flap over the cut end of the tibia, and at rendering a more suitable stump for a patellar tendon weight bearing prosthesis. The author has used this technique consistently for several years. The results have been extremely encouraging. It is suggested that its adoption as a routine method would benefit the surgeon, the prosthetist, and the patients alike.

Indications

All cases where a sound weight bearing plantar surface can not be obtained. Syme's and Pirogoff's amputations offer no real advantage. The indications for their use are largely social and psychological, particularly in communities where there are strong objections to losing any part of a limb. These operations are technically more difficult, and they yield a considerably lower percentage of good results.

Contraindications

1. Poor skin in the proximal one-third of the lower leg. Particular emphasis must be placed on the condition of the skin in the patellar tendon region, which will take most of the weight when the prosthesis is worn.

2. Chronic pre-patellar bursitis. This condition—to historically interested surgeons known as "house maid's knee"—is fairly common in communities where the women kneel down while grinding maize flour or while performing similar duties. Usually this is a relative contraindication, since careful excision of the aseptically inflamed bursa with meticulous skin suture may permit a patellar tendon weight bearing prosthesis to be fitted.

3. Infection, extending above the lower one-third of the lower leg. Again this is frequently a relative contraindication, which can be overcome with correct treatment of the original condition.

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4. Degenerative oseto-arthrosis of the knee. Even if full extension of the knee is possible, such a condition will not permit a weight bearing prosthesis on an extended knee. One of two underlying conditions will usually be found. One is impairment of pain sensation around the knee and/or impairment of proprioceptive sensation of the knee structures. These conditions tend to produce a joint that is too unstable for a patellar tendon weight bearing prosthesis. A prosthesis with weight bearing thigh corset and lockable knee joint is undoubtedly the best answer. But this presupposes a standard of prosthetics that is not available to most of our patients. The other condition is intra-articular degeneration consequent on long standing contracture of the knee joint. Subluxation of the knee joint, very commonly seen in long standing contractures of the knee following post-polio quadriceps paralysis, is not a dominant feature in leprosy, but should nevertheless be definitely excluded before below knee amputation is undertaken.

Detailed radiographic evaluation of the knee joint may not be possible. Clinical assessment is normally sufficient. The following points must be fulfilled in order to ensure a below knee stump, suitable for a patellar tendon weight bearing prosthesis:

full, active extension of the knee joint,
lateral and antero-posterior stability of the knee joint,
the stump must have sufficient coverage of good quality tissue,
the length of the stump, measured as length of bone, must be at least 10 cm from tibial tuberosity to cut end of tibia.

A considerable proportion of our patients have a poor sense of balance. This may be due to a "psychological amputation" of an anaesthetic limb. It may also be due to deficient proprioceptive responses. It may also be due to long standing inactivity of a grossly damaged extremity or to a general despondency of the patient. This in itself is not a contraindication to amputation, but it makes the training of the patient a much more difficult and drawn out procedure.

It is worth remembering that gross infection of the foot, particularly if it involves the weight bearing surfaces, is likely to trigger off "reactions", and is also likely to be the cause of gross anaemia and protein deficiency. Much can be gained by formal amputations in spite of such obvious, general contraindications.

Recommended Technique

1. Spinal anaesthesia is recommended. Since it is unpleasant– to say the least–for anyone to listen to the saw cutting through his own bones, a fairly heavy premedication is advisable. In our experience pethidine, 100 mg, and chlorprometazine, 50 mg, given subcutaneously one half hour before arrival in the theatre is sufficient to let the patient sleep peacefully during the operation.

2. A pneumatic tourniquet is applied to the thigh. It is secured with a completely covering non-elastic bandage. After the anaesthesia has taken effect, and the required skin preparation has been completed, the leg is elevated steeply for a few minutes, and the tourniquet is quickly inflated to Hg 300 mm.

3. Base points for the skin incisions:

(a) The selected point of division of the tibia (this should be 10-20 cm distal to the tibial tuberosity),

(b) A point 3 cm proximal to point a on the anterior border of the tibia,

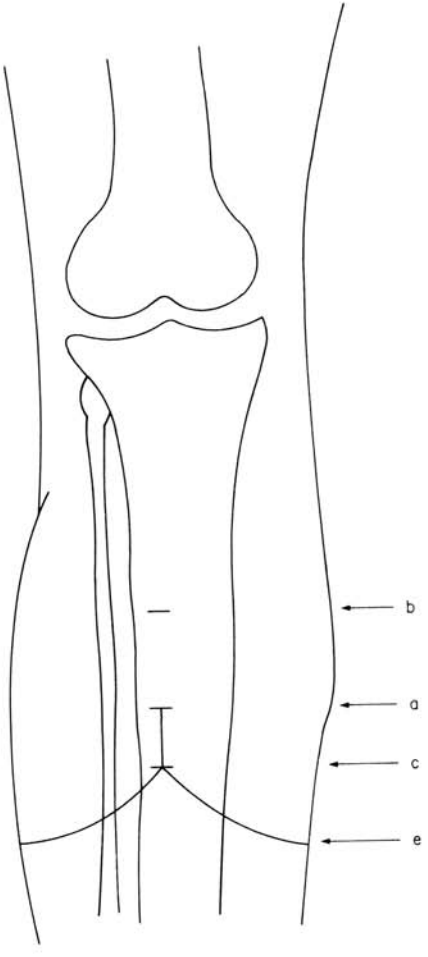

Fig. 1. Frontal view of the lower leg, showing the line of incision.

(c) A point on the anterior border of the tibia, 2 cm distal to point a,

(d) A point directly posterior to point a,

(e) Points in the exact mid-line of the lower leg, one on the medial one on the lateral side, both at the same height, 4 cm distal to points a and d.

4. Skin incisions are carried straight through skin, subcutaneous tissue, and muscle fascia. The line of incision is from point a through c, then in two diverging cuts through points e to point d.

5. The two semicircular flaps are raised and freed from underlying muscle for only 2 cm. At this level the muscles are divided across. The proximal leg of the incision is carried through periosteum, which here is continuous with the muscle fascia. Major vessels are caught and ligated as they are met. Periosteum is scraped

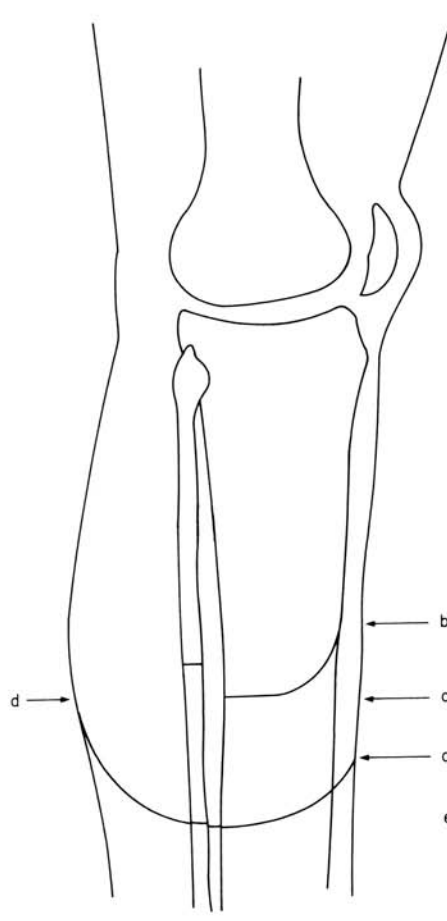

Fig. 2. Lateral view of the lower leg, showing the line of incision, and the division of tibia and fibula.

back on the tibia to point b. The tibia is divided at point a, after which the anterior point is cut down obliquely to minimize chances of pressure necrosis of the skin. The fibula is divided 1 to 3 cm above the level of the tibia cut. This ensures a cylindrical stump, which is more suitable for a patellar tendon weight bearing prosthesis than the classical, conical stump.

6. The leg is then elevated, and the tourniquet removed completely. Remaining bleeding vessels are visualized and ligated.

7. The muscle fascia is sutured in interrupted, buried knots. Any material, except silk, is acceptable, if not too heavy. No attempt is made at muscle suture. The muscles are still attached to the muscle fascia, and they fall neatly in place under the fascia suture. Skin is sutured, preferably using monofilament stainless steel wire or monofilament synthetic material. A neat skin suture is essential. If

the skin incisions have been placed correctly, the resulting stump is cylindrical with a suture line running in the sagittal plane. Any small dog's ears should be left untouched, since their removal may jeopardize the blood supply. Anyway they invariably disappear later. If the muscles and bones have been divided correctly in relation to the skin incisions, the subfascial tissue will be under just sufficient tension to prevent the formation of dead space with the inherent danger of haematomas. Drains are therefore unnecessary. Indeed they will interfere with the neatness of the suture line, and may act as ports of entry of postoperative infections.

If the surgeon is not sure of the right level of incision, it is wiser to cut too generous flaps, both of muscle and of skin. These can always be cut back to correct size. Too short and too tight flaps on the other hand can only be corrected by cutting back the bone, which interferes with the function of the prosthesis.

8. Remaining oedema and blood is expressed, and the stump is covered with generous gauze pads, including the knee. A thin plaster of Paris shell is moulded round the stump, including the distal part of the thigh, with the knee fully extended.

9. In the ward the stump is kept elevated for 48 hours. From the third day the patient can start isometric quadriceps exercises.

10. The plaster shell is removed on the 14th day, and the patient can start active knee exercises against increasing resistance. The stump is covered in formative bandage.

11. The sutures are removed on the 21st day. Stump bandaging continues.

12. Approximately 4 weeks after the operation the patient can usually be fitted with the first prosthesis. It is important to keep in mind that the stump will remodel and shrink while this first prosthesis is worn. A second prosthesis should not be considered a failure, but rather a necessity of the technique.

This amputation technique was originally developed for geriatric patients with ischaemic necrosis and sclerotic arteries. Under these conditions the use of a tourniquet is strictly contraindicated. Elevation of the stump postoperatively is likewise avoided. While these points do not arise from leprosy per se, nevertheless a number of our patients may fall inside the group where these precautions are indicated.

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News and Notes

NEW WHO CAMPAIGN AGAINST SIX TROPICAL DISEASES

The WHO Special Programme for Research and Training in Tropical Diseases came under close scrutiny during a recent meeting of heads of agencies and national representatives. As a result, 6 tropical diseases were chosen as the targets for a massive international campaign directed towards their treatment and prevention, and extending over the next 10 years. The 6 diseases chosen were: malaria, schistosomiasis (bilharziasis), filariasis including onchocerciasis (river blindness), trypanosomiasis (both sleeping sickness and Chagas disease), leprosy and the different forms of leishmaniasis (kala azar, tropical ulcer).

Dr H. C. Goodman, the Director of WHO's Special Programme, said that as it was impossible to approach all the known tropical diseases, the initial attack was being focussed on 6 chronic debilitating diseases, and pointed out that the programme would be particularly concerned with attracting more scientists in fields like immunology, and cellular and molecular biologists to the study of parasites.

During the 2-day meeting it was stressed that although Africa had been chosen for the initial attempt to bring these plagues within control, the Special Programme is not simply a continental effort but a global one, since all 6 diseases also afflict huge areas elsewhere. The diseases would be studied on their own ground in the tropical countries to ensure that the remedies are tailored to the real needs and not to the supposed needs of the countries concerned. As a result, scientific training and expertise will be developed that can be used to help apply the remedies, to adapt them or to develop new ones wherever in the world these diseases are rampant.

Substantial contributions to support the multi-million dollar programme were pledged by a number of donor countries during the course of the meeting.

COUNCIL OF WORLD ORGANIZATIONS INTERESTED IN THE HANDICAPPED

As one of the 37 member-organizations of CWOIH, the International Leprosy Association was represented by its Secretary-Treasurer (Dr S. G. Browne) at a meeting of the Council held in Geneva on September 23 and 24. The United Nations sent its representative to the meeting, as did also the World Health Organization, UNICEF, UNESCO and the International Labour Office.

The size of the problem of the handicapped in the world is indicated by the numbers—a total of 400 million, of whom perhaps 300 million are in the developing countries; of the latter, only about 1% are at present within reach of any physical and social assistance, and most of these live in the capital city or the larger towns. Leprosy is, of course, a prime example of disabling handicaps that

are compounded by high degrees of social discrimination. Emphasis was laid on the need to concentrate on the preventive measures that should take precedence over expensive schemes for rehabilitation, even in organizations whose main objects are the relief of the consequences of existing handicapping conditions. A rather disturbing report was presented that in one instance (which may or may not be representative), an excellent project for helping handicapped persons led to a greater eventual dependance on medical care and a lowered industrial productivity when the group was compared with another group in similar circumstances where rehabilitation services were not offered.

The discrimination practised against the handicapped was the subject of debate: in employment, housing, schooling and access to social services, the handicapped are often penalized. In many countries leprosy sufferers find themselves in a special category of deprivation. The Council may make official representations to the United Nations on behalf of the handicapped in the hope that their status may be recognized and raised.

XIII WORLD CONGRESS OF REHABILITATION INTERNATIONAL

A leprosy session will be organized at this Conference, to be held in Tel Aviv, Israel, from June 13 to 18, 1976. Those wishing to take part are requested to get into touch with

Dr S. G. Browne,
57a Wimpole Street,
London, W1,

for the purposes of the leprosy session, and with

Dr E. Chigier,
Chairman of the Organizing Committee,
PO Box 16271,
Tel Aviv,
Israel,

for details of registration, etc.

PHYSICAL THERAPY IN THE TREATMENT OF LEPROSY (HANSEN'S DISEASE) LECTURE NOTES FOR USE IN PHYSICAL THERAPY TRAINING SCHOOLS

Some years ago, the World Confederation for Physical Therapy published a small (28 pages) booklet written initially to help teachers and tutors in training schools throughout the world in preparing lectures and demonstrations for their physiotherapy students. A shorter section is intended for use in countries in which leprosy is not endemic, but the longer section gives rather detailed material that should prove invaluable to teachers who might feel themselves ill prepared to deal with such a subject.

A French edition has proved popular in French-speaking countries.

A Spanish edition is available, and should prove equally useful.

A small charge (of 10p) is made, plus postage. Enquiries should be addressed to:

Miss E. M. McKay
World Confederation for Physical Therapy,
Brigray House,
20/22 Mortimer Street,
London W1P 1AA.

DAMIEN-DUTTON AWARD 1975

At a recent ceremony in New York Dr Oliver W. Hasselblad became the 23rd recipient of the Damien-Dutton Award. Following 20 years service as a medical missionary in India, Dr Hasselblad joined the staff of the American Leprosy Missions in 1959, and became widely known during the following 15 years for his tireless advocacy of deeper concern for the social welfare and rehabilitation of leprosy sufferers. He served as a member of the WHO Leprosy Expert Committee and played a prominent role in succeeding International Leprosy Congresses. He has travelled widely, and his assessments of leprosy needs in developing countries have resulted in important changes in many areas, with control programmes replacing institutionalized care. Dr Hasselblad is a member of the Council of the International Leprosy Association, and is the present executive officer of the *International Journal of Leprosy.* We offer Dr Hasselblad our cordial congratulations and best wishes.

TRANSMISSION OF PATHOLOGICAL MATERIAL BY POST TO AND FROM THE UK

Recent correspondence in the *Lancet* has drawn attention to the possible danger to the public caused by poor packaging of pathological specimens sent through the post. The Principal Medical Officer to the British Post Office has drawn attention to the following regulations.

Pathological specimens may be sent only by first class letter post and must be packaged and labelled in a prescribed manner. Any such packet found in the parcel post or found in the letter post not properly packed and labelled will be destroyed. Requirements for packaging pathological specimens are:

the liquid or substance must be enclosed in a container which is hermetically sealed or otherwise securely closed,

the container must be placed in a strong wooden or metal case (any other case must be approved by the post office before use) in such a way that it cannot shift about,

the container must be surrounded by enough absorbent material—sawdust or cotton wool—to prevent any leakage from the package if the container becomes damaged,

the outside of the package must be marked "Fragile with care" and "Pathological specimen".

1976 TRAINING COURSES AT KARIGIRI

Dr Fritschi, Superintendent of the Schieffelin Leprosy Research Centre, Karigiri, S. India, announces the following schedule of training courses during 1976.

Categories of training	Duration	Date of course
I. FOR DOCTORS		
(a) Condensed course for doctors engaged in part time leprosy work	One week	January 19-24 November 15-20
(b) Medical students' course	One week	June 14-19
(c) Medical officers' training course	Six weeks	Feb. 16-Mar. 27 July 19-Aug. 28
(d) Ophthalmic aspects of leprosy	One week	Feb. 9-14
(e) Inservice training—in Medical Surgical, Ophthalmic, Pathology and Control	by arrangement	
II. FOR NURSES, PHYSIOTHERAPISTS, OCCUPATIONAL THERAPISTS, SENIOR PARA-MEDICAL WORKERS, HEALTH EDUCATORS, ADMINISTRATORS, etc.		
Non-medical supervisors course (Govt. of India curriculum). A full comprehensive course in leprosy for those engaged in full time service.	4 months	June 7th-Sep.
III. FOR OTHERS		
(a) Para-medical workers (non-medical assistants—Govt. of India curriculum)	6 months	April 5th October 4th
(b) Shoe-makers' course	4 months	by arrangement
(c) Prosthetic technicians	18 months	January 1st wk. July 1st wk.
IV. SOCIAL AND REHABILITATION WORKERS		
A short orientation course in the special precautions required for persons with anaesthetic hands and feet.	One week	Sept. 20-25

Food and accommodation will be provided on payment. For further details and prescribed application, please contact the Training Officer, SLR Centre, (PO) 632 106, Tamil Nadu, South India.

ALL AFRICA LEPROSY AND REHABILITATION TRAINING CENTRE (ALERT)

VACANCY FOR A TRAINING DIRECTOR

A physician is required to succeed the present Training Director of the above Centre in Addis Ababa.

Preference will be given to an experienced leprologist. The successful candidate will be interested in teaching at all levels, familiar with or prepared to learn current educational principles and methods, and will assume overall responsibility for the organization and supervision of courses and for the progress, evaluation, and follow-up of students. The courses presently given at ALERT include: leprosy control and clinical leprosy for doctors, courses for rural area supervisors, seminars on teaching of medical auxiliaries, leprosy control for expatriate medical auxiliaries, and physiotherapy in leprosy for physiotherapists.

The language of instruction is English but proficiency also in French would be an advantage. In addition to the specific responsibilities for the training function of ALERT, the successful candidate will be expected also to share in research and service activities.

The post is sponsored and a tax-free salary of Eth.$26,400 or more subject to negotiations) per annum is recommended. Free housing with hard furnishing is provided, together with transportation to and from Ethiopia.

Applications, with curriculum vitae and names of three referees, to be sent to the Executive Director, ALERT, PO Box 165, Addis Ababa, Ethiopia, before 14 February, 1976.

MEMORANDUM ON LEPROSY CONTROL

The Leprosy Mission have advised us that copies of Dr Browne's booklet, *Memorandum on Leprosy Control,* published in 1971, second edition 1972, are still available gratis from the Editorial Department, The Leprosy Mission, 50 Portland Place, London W1N 3DG.

ARCHIVES OF THE LEPROSY MISSION, HAY LING CHAU LEPROSARIUM, HONG KONG

The Leprosarium run by The Leprosy Mission on the island of Hay Ling Chau, Hong Kong ("The Isle of Happy Healing"), closed down in January 1975. At the beginning of January there were 93 patients, of whom 42 returned home or to accommodation found for them and 51 were transferred to the Lai Chi Kok Hospital under the care of the Hong Kong Government Medical and Health Department. The Leprosarium was started on the 6th August, 1951, when Dr Neil Fraser and 22 patients landed on a bare and deserted island. It developed through the years into a large and beautiful institution where 540 patients received excellent medical and surgical attention and lived in a community where all their needs—physical, mental, recreational and spiritual—were cared for. From beginning to end, 2305 patients were admitted, almost all of whom were Chinese. Those admitted were suffering from lepromatous or borderline leprosy or required hospitalization for acute illness, ulcers or surgery.

Throughout the years full and careful records were kept of each patient and as the closure approached it became a matter of concern that these records should not be destroyed or dispersed, but should be made available both to those responsible for continuing treatment and those wishing to pursue serious research. After discussions the Hong Kong Government Archivist kindly agreed that the entire collection of records pertaining to all patients who had ever been treated at Hay Ling Chau should be transferred to the Public Records Office, Hong Kong.

The transfer took place between January and June 1975 and the records are now indexed and stored in the new, air-conditioned premises of the Public Records Office.

The records transferred include, for each patient: diagnosis; medical history; treatment procedures; physiotherapy; surgical procedures; radiography—x-ray films and reports; laboratory reports; eye examinations; photographs; and in some cases colour transparencies, skin smear and biopsy slides. These records are all linked by the Leprosy In-Patient number (LIP) given to each patient on admission to Hay Ling Chau Leprosarium and recorded in the Admission Register. In addition there is much supporting literature both concerning the history and general development of Hay Ling Chau, and concerning special investigations carried out there. All of this material has been fully and carefully indexed and listed by the Archivist and copies of the catalogue* may be seen at:

1. The Leprosy Mission, 50 Portland Place, London W1N 3DG, England.
2. The Leprosy Mission, Hong Kong Auxiliary, 33 Granville Road, Kowloon, Hong Kong.
3. The Public Records Office of Hong Kong, 2 Murray Road, Hong Kong.

The whole collection is closed and is not available to the general public since most of the individuals concerned are still alive: many of them are still receiving follow-up treatment and their privacy must be protected. However, access to the records may be allowed in the following instances:

1. When the records are required for the treatment of individual patients application must be made to the Public Records Office through the Director of Medical and Health Services, Hong Kong Government.
2. For those who wish to make use of the records in pursuing original research into leprosy, application should first be made to the International General Secretary, The Leprosy Mission, 50 Portland Place, London W1N 3DG, stating the object of the research and the data required.

We record our sincere gratitude to the Hong Kong Government and its Archivist for storing, indexing and making available this unique body of material.

Alan D. Waudby,
Assistant Secretary, The Leprosy Mission
(formerly Representative for East Asia).

DR S. G. BROWNE C.M.G

Dr Browne, Consulting Editor to this Journal, was awarded the Honour of Commander of the Order of St. Michael and St. George in the New Year's Honours List, 1976, an entirely fitting recognition of the great distinction with which Dr Brown has served the cause of those who suffer from leprosy. We are proud to join our congratulations to those of his numerous friends in many countries.

* Public Records Office of Hong Kong: *Archives of The Leprosy Mission Hong Kong Auxiliary, Hay Ling Chau Leprosarium. 6th August, 1951-22nd January, 1975.* HKMS 2 May, 1975.

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Obituary

DR VINCENT C. BARRY
D.Sc., Sc.D.(Hon.), M.Sc.

With the death of Dr Barry on 4 September, 1975, the world of chemotherapeutic research has lost one of its most brilliant intellects, and leprosy sufferers will mourn a real benefactor.

Vincent Barry was born in Cork (Eire) in 1908. Twenty years later, he graduated in chemistry from University College, Dublin, gaining first place. A year later, he obtained the degree of M.Sc., and 10 years later—as assistant to the Professor of Chemistry at University College, Galway—his doctorate in chemistry.

In 1941, Dr Barry was awarded a research fellowship in organic chemistry tenable at the newly-created Laboratories of the Medical Research Council of Ireland, with a special remit of the investigation into the chemotherapy of

tuberculosis. In the course of the next few years Barry, together with the brilliant colleagues he gathered round him (notably Dr M. L. Conalty and the 2 others who had all been working with him for more than 25 years), synthesized numerous compounds and tested them *in vitro* and *in vivo* for their antimycobacterial activity.

Barry "came into leprosy" with the synthesis of compound B283, which was shown to be active against the disease in a small series of cases in Eastern Nigeria. From 1950 onwards, in the more adequate laboratory facilities made available to him and his team at Trinity College, Dublin, Barry embarked on a most fruitful period, during which his flair for research and his monumental knowledge of his own field of synthetic chemistry resulted in the production of scores of compounds based on the rimino-phenazine nucleus. In 1957, a compound known as B663 was developed in this series. It showed remarkable properties of causal prophylaxis in experimental mouse tuberculosis. Even more interesting—from the standpoint of its eventual use in leprosy—was its concentration in macrophages. It was this property that attracted the attention of R. G. Cochrane and then of S. G. Browne.

During discussions on its antimycobacterial properties, Barry said, "B663 is tailor-made for leprosy—it goes where the bacilli are. To judge by its action in the mouse, it should stop your bacilli multiplying. Why not try it on patients?"

After going into the excellent work on animal toxicity tests, drug concentration in tissues, long term absence of carcinogenicity, and dose levels, Cochrane and Browne agreed that it was justifiable to use the drug on human volunteers in the Uzuakoli Leprosy Research Unit, Eastern Nigeria. The rest is a matter of history. With Hogerzeil as co-worker, Browne was able to report on the mycobacteriostatic, and then the anti-inflammatory properties of B663. The manufacturers were persuaded to make a further quantity of the drug for investigative purposes. And now, clofazimine (Lamprene, Geigy) is acknowledged to be an excellent leprostatic drug, with definite indications in lepromatous leprosy.

Not content with synthesizing B663, Barry and his team went on to develop new rimino-phenazine compounds, one of which—B1912—promises well in basic experimental work, and should be less expensive to manufacture on a commercial scale.

The team also became interested in the chemotherapy of neoplastic disease, making several important contributions to research in this field. In 1968, Barry's work was honoured by the award of the Boyle Medal for "exceptional merit in the domain of pure science". In his Boyle Lecture, he traces the fascinating development of his saga of synthetic chemistry, culminating in the production of B663 and B1912.

Once Barry had become attracted to leprosy, and involved in the drug trials of B663, his interest never flagged. He became a member of the International Leprosy Association and attended the Congresses in London and Bergen. His genial presence and broad Irish brogue endeared him to many who were seeing the clinical results accruing from the use of the compound that he had synthesized in Dublin years before.

We salute a good man whose brilliant researches have brought new hope to many sufferers from the most distressing forms of leprosy. And we express our condolences to his widow and their 6 children.

S. G. BROWNE

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Leprosy and the Community

WORKSHOP ON THE PROMOTION OF LEPROSY WORK IN INDIA, AUGUST 1975

Closer co-ordination between government and voluntary agencies in India in leprosy control has been encouraged through a Workshop convened by the National Institute of Public Cooperation and Child Development, with the cooperation of the National Leprosy Organization (India), the Hind Kusht Nivaran Sangh, The Leprosy Mission and the Gandhi Memorial Leprosy Foundation. The main objectives of the Workshop were to review the needs and programmes of government and voluntary agencies in India; discuss the role of government and voluntary agencies in this field; suggest ways and means of streamlining existing programmes; and evolve a strategy for maximal cooperation at all levels. Background and discussion papers were presented by experts in various aspects of the subject. The Report of the Workshop includes the following conclusions and recommendations.

1. There was a general appreciation of the efforts of the Government and Voluntary Organizations in the field of leprosy control. However, the Workshop took a serious view of the fact that so far only one third of the existing cases have been recorded for treatment and only about 50 per cent of the population in the endemic areas have been covered by the National Leprosy Control Programme. It recommended that in order to ensure effective interference with the transmission of infection, all the existing cases of leprosy should be brought under treatment, and the entire population in the hyper-endemic and moderately endemic areas should be covered by the programme as quickly as possible in order to ensure effective case detection in the early stages.

2. The Workshop recommended that the prevalence and incidence rates of leprosy should be studied through systematic surveys in both the covered and uncovered areas of the country. More precise knowledge about these rates is necessary to assess the need for the services in different regions and the impact of the programme in the areas covered by it.

3. Arrangements should be made for hospitalization of infectious, sulphone resistant and refractory cases in order to contain the disease. Adequate provision should be made for hospital beds and expansion of facilities like physiotherapy, reconstructive surgery and occupational therapy.

4. At present DDS is the sheet anchor in the treatment of leprosy. However, it has been found that some patients are developing DDS resistance and sensitivity to the drug. Therefore there is urgent need to provide alternative drugs and make them available at a reasonable cost in adequate quantity to ensure their regular supply.

5. As leprosy control services have to be provided on a very extensive scale, the

ultimate objective should be the integration of leprosy work with the general health services in the country. The existing institutional structure at different levels should be utilized for providing them in areas where they are needed.

6. At present the medical courses at graduate level do not impart sufficient knowledge about leprosy. This is responsible not only for relative ignorance of an average medical graduate about this disease but also his unwillingness to work in leprosy control programme or to handle leprosy patients in the general hospitals. The Workshop strongly recommended that the curricula of medical colleges should be suitably revised to impart adequate knowledge about leprosy to the students and interns to inculcate in them a positive attitude towards leprosy work. It was further recommended that facilities for training in reconstructive surgery, which is an attractive field of study, should be expanded in the medical colleges. This would ultimately strengthen the existing facilities for this specialized service in the hospitals and facilitate effective rehabilitation of leprosy patients.

7. While expanding the leprosy control programme it should be ensured that properly trained medical and para-medical workers in adequate numbers are available for running the programme. In fact, the training of workers should precede the opening of Leprosy Centres. Arrangements should also be made for the in-service training of the existing staff wherever necessary. The curricula for the training of para-medical workers should be suitably revised to include social welfare, health education and rehabilitation procedures. Refresher courses for existing leprosy workers and general health workers should be organized.

8. The Workshop recommended that the work of Leprosy Control Units should be adjudged on the basis of the following criteria: (i) Case detection by total population surveys every 3 years with at least 90% coverage; (ii) Not less than 80% of infectious cases brought under regular treatment; and (iii) Deformity index in newly detected cases should come down year by year and should not ideally be more than 5% of cases in 10 years.

9. The Workshop emphasized that in a comprehensive leprosy control programme, the measures which would help prevent the development of deformities should be given as much importance as the efforts to help the patients make the maximum use of their residual capacities to become useful members of the community. The former would ultimately make rehabilitation easier.

10. The leprosy patients have psychological resistance to rehabilitating themselves, and their own family members and the people in the community also do not accept them as normal human beings. These problems need to be tackled through programmes of individual counselling of the leprosy sufferers and education of the family members and the community in general. But the Workshop emphasized that any programme which helps leprosy patients become economically productive and independent is likely to be far more effective in their rehabilitation than efforts to change the attitudes alone. Therefore programmes of economic rehabilitation should be given due weightage.

11. The Workshop identified 2 distinct groups of leprosy sufferers from the point of view of their rehabilitation needs. The first group consists of those who can be helped to regain their capacity to do some productive work and can live with their families as earning members. They need vocational training and economic assistance to become independent. The other group consists of those for whom there is no hope to earn their own subsistence. They need a monthly allowance from an outside agency and therefore the Government should help

them with programmes of social assistance. The rehabilitation programmes should be so designed as to cater to the needs of both these groups.

12. The Workshop considered education of the community about the medical and social aspects of the problem of leprosy as one of the most important components of a sound programme for its control and rehabilitation. The masses need to be informed about the nature of the disease to remove the wide-spread ignorance, prejudices and fears about it. Suitable efforts in this direction would not only help prevent spread of infection but also facilitate the rehabilitation of leprosy patients. Scientific lessons about leprosy should be included in the school curriculum from the primary stages. In addition, the mass media like the newspapers, radio and TV should be fully utilized for disseminating scientific information about leprosy and making people aware about their responsibility towards leprosy patients.

13. The Workshop felt that it was neither possible nor desirable to draw a very rigid line between the responsibilities of voluntary organizations and Government in the field of leprosy control and rehabilitation. However, considering the strengths and limitations of these 2 agencies, it was recommended that the primary areas of government concern should be research, policy formulation, training, massive control programmes, financing and evaluation, and those of voluntary concern should be health education, public cooperation, dissemination of information on policies and programmes, welfare and rehabilitation of patients, etc. in addition to leprosy control work.

14. The discussion in the Workshop revealed many gaps in the information of representatives of voluntary organizations about the Schemes of the Central Government under which voluntary organizations can get financial assistance for extension of hospital facilities, purchase of equipment, rehabilitation programmes, etc. It was recommended that the concerned Departments at the Central and State levels should circulate their Schemes as widely as possible and evolve ways and means to ensure that the information reaches the organizations in time so that they can avail themselves of the assistance, and the funds provided in the budget do not lapse.

15. The Government Scheme for Leprosy Control Unit, SET Centres including the voluntary SET Scheme should have an element of flexibility so that they can be adapted to local conditions. It was specially stressed that if the norms given in the SET Scheme about the population to be served by a Centre are observed rigidly in tribal or hilly areas, which are sparsely populated, the very purpose of the Scheme is likely to get defeated. Therefore, the Workshop recommended the Government to make suitable modifications in the Scheme considering the special problems in hilly and tribal areas. Similarly, necessary flexibility should be introduced in the terms and conditions attached with various grant-in-aid Schemes.

16. The Workshop recommended that the State Governments should constitute Leprosy Advisory Committees on the lines of the Central Leprosy Advisory Committee which is already in existence. The Committee should consist of representatives of Government and voluntary organizations, leprologists and social workers. It should function as a forum for discussion on problems of leprosy control and rehabilitation, an instrument for coordination at the State level and an expert body to advise the Government. A sub-committee of this body should provide technical guidance to voluntary organizations in the State.

17. The Workshop recommended that there should be more active and

effective communication between the Centre, the State and the field agencies for better implementation of Control programme and optimum utilization of available resources. This should be followed up by frequent dialogues, regional meetings, State level conferences and visits by the representatives of the Centre to the States. The Workshop further felt that at the meetings of Central and State Ministers of Health, adequate time should be allowed for review of work done in the field of leprosy.

18. In order to cope with the rapid expansion of the Leprosy Control Programme, Leprosy Cells at the Centre, State and District levels should be adequately staffed and equipped in order to ensure effective programme management. More specifically, Leprosy Officers at Centre and States should be given adequate administrative support so as to enable them to discharge their supervisory and field monitoring responsibilities more effectively.

19. The Central Health Ministry may issue firm guidelines about the minimum qualifications and experience of Leprosy Control Work needed for the post of State Leprosy Officer and Para-Medical Supervisor.

20. In order to attract and retain qualified medical personnel in leprosy control work Government should offer adequate incentives in terms of special remuneration and facilities, as well as priority in selection for Post-graduate courses to Medical Officers engaged in leprosy work.

21. The Workshop considered the need to bring about greater coordination among Voluntary Agencies functioning in the field of Leprosy Control Work. This is specially necessary in order to organize mutual aid and assistance through agencies best suited to provide specific types of help needed.

The Workshop, therefore, recommended that Hind Kusht Nivaran Sangh national headquarters should take the lead in providing coordination and serve as the Central coordinating agency, without merging the independent identity of cooperating organizations.

HIND KUSHT NIVARAN SANGH (INDIAN LEPROSY ASSOCIATION)

Annual Report for 1974

The Annual Report of the Hind Kusht Nivaran Sangh for 1974 makes encouraging reading. The National Leprosy Programme is now geared to rapid development during the 5th Five Year Plan, and the project for its assessment under the Indian Council for Medical Research is now in operation. The Sangh is making its own very important contribution through encouraging coordination between government and voluntary agencies, supporting training courses for physiotherapy technicians, orientation courses for medical officers, health education, rehabilitation and publicity, especially through its own 37 publications. The Sangh took the lead in publicizing World Leprosy Day in India, in association with which 750,000 "leprosy seals" were sold. *Leprosy in India* is the official organ of the Sangh, and has continued to progress under the Editorship of Dr Dharmendra. The Professor K. C. Sahn Gold Medal for the promotion of research in leprosy has been instituted, with the first award presented to Dr D. K. Job of Christian Medical College and Hospital, Vellore. With over 3 million leprosy sufferers in India, the Sangh has a very important role to play, and we extend greetings and best wishes for its continued prosperity during 1976.

DEATH AND REBIRTH OF A LEPROSY SERVICE

RICHARD C. BROWNE*

The past 15 years witnessed the disintegration of several leprosy services in Central Zaire. Programmes of case finding, treatment and rehabilitation that were at one time among the most respected in Central Africa, have vanished. Two unrelated events coincided at one point in time to produce this unfortunate situation. First, the independence proclaimed in 1960 released a wave of social unrest which culminated in the intertribal wars of the mid 1960's. There was interruption of communications; transport of supplies and personnel was hindered. Medical workers and patients located in some areas were forced to flee to their homelands. Records were destroyed and clinics were shut down. Treatment became sporadic and patients were lost.

Second, the closing of leprosy villages or "colonies" came into fashion. Ambulatory home treatment was encouraged and adopted. Patients were sent back to their villages. Appointments may have been made for their periodic return; but the danger of travel and the deterioration of roads precluded this from happening regularly. These events took place at Bulape in the West Kasai province.

Bulape, an isolated mission hospital, was established in 1920. For years it had received leprosy patients brought in by Belgian sanitation workers from village screening surveys. The estimated prevalence of leprosy for the area was greater than one per thousand inhabitants. Missionary physicians at Bulape cooperated with government workers in standardized treatment practices. Eventually a colony of leprosy patients grew up adjacent to Bulape Hospital. A separate clinic building was constructed. A leprosy nurse was appointed. Special gifts of food and clothing were donated to the patients by missionaries and by philanthropic societies. At its apogee in the 1950's there were several hundred resident leprosy patients under treatment at Bulape.

In 1960 the country was declared independent of Belgium. Sanitation workers withdrew and were not replaced. New admissions to the leprosy service at Bulape fell off. Younger missionary physicians arrived who were not accustomed to the ways of managing a leprosy service. The leprosy nurse departed; and ongoing leprosy care was "integrated" into the general outpatient clinics of Bulape Hospital. In 1964 there was renewed intertribal fighting with bloodshed in the Bulape area. Physicians were evacuated temporarily. Treatment was interrupted and many patients fled. Soon thereafter, the leprosy colony was closed. The 25 patients who remained were sent away. All of them actually departed except a handful of old, non-active cases with deformities. These people simply moved 1 kilometre away and continued a wretched existence without special consideration or care.

When the author arrived at Bulape in 1973 he found no records of old or present leprosy cases. There were no active cases known. Five elderly people with deformed feet and hands constituted the entire leprosy case load. They earned a meagre living by making charcoal and selling it to the local citizens. Bulape Hospital itself was a thriving institution. It consisted of 100 beds. It offered full obstetrical and surgical services. There was an active paediatric unit complete with

* *Bulape Hospital, Kananga, Zaire.*
Received for publication 16 October, 1975.

a nutrition rehabilitation centre. Road teams touched some 20,000 people in a rural community health programme. Yet in spite of all this clinical activity, the leprosy service at Bulape was dead!

The American Leprosy Missions (ALM) encouraged a rebirth of this service. For the new missionary physician, ALM underwrote 1 month's specialized training in Addis Ababa (ALERT). ALM then secured a lift of $6000 for equipment, transport, and personnel development over a 3 year period. The new service was to be integrated with the community health project at Bulape. A male nurse was recruited. He was sent for training at Kivivu, Zaire; and guaranteed a salary commensurate with his specialized training and responsibility.

The primary goal of the resurrected leprosy service is to find and to place under treatment all active cases of leprosy in the Bulape area. To do this required the establishing of a reputation of confidentiality, kindness and effectiveness. The 5, old burnt-out cases were helpful in doing this. They were brought to the out-patient clinic for skin care and physical therapy. The new nurse won their respect. Soon, other old cases showed up. Then a person with active lepsory came in, was examined, educated in his disease and sent home with medicines. He has continued to return for routine follow-up. As the reputation of the revived leprosy service spread, more people came in. Some with non-leprous lesions felt free to present for diagnosis of other skin problems.

Next, a series of village screening surveys was organized as a part of the community health effort. People were invited to appear for "skin inspection"; most do not fear this procedure if done discreetly. More and more people with active disease were discovered and enrolled. Although patients were often asked to come to the hospital for biopsy or other diagnostic studies, all were left in their home village for treatment.

In the 1½ years since the Bulape leprosy service was re-born, 4 additional treatment posts have been set up. These posts allow patients to be examined and treated closer to their homes. At the time of writing 135 leprosy patients are enrolled and under surveillance. Most patients follow their treatment satisfactorily. They appear pleased with the care they are receiving.

The future of this modest programme requires its merger with the general services of Bulape Hospital. Classes and demonstrations conducted by the physician and leprosy nurse have now begun to familiarize other hospital workers with the diagnosis and management of the disease. It is clear though, that this revival of interest in leprosy could not have been accomplished without personnel with specialized training. Without someone on the staff whose primary concern is leprosy, the service would again be relegated to a low priority. The leprosy service at Bulape would then die a second death.

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Field Worker's Forum

PSYCHOLOGICAL ASPECTS OF LEPROSY

T. F. DAVEY

Leprosy is unique among infective diseases in the intensity and persistence of its emotional content. Every leprosy patient is a person under stress, and the doctor's acceptance of this and sympathetic reaction to it underlie any success we may achieve in dealing with this disease. The psychological aspects of leprosy thus need to be thought of in relation both to the patient and the doctor himself.

The Patient

Stress in the leprosy patient derives from 3 main sources.

1. *The stress of inherited ideas.*

It is of profound importance for the health and wellbeing of most people that they should be accepted by their fellows and play their part in their community. Without this there is no enduring happiness or fulfilment, and rejection by the community is the ultimate calamity. Long ago in the history of mankind a group of conditions was identified which merited such rejection. These were of two sorts. One was criminal conduct which threatened the structure of society. The other was disease which seriously threatened the life of others either at the physical or spiritual level. Leprosy, with its mysterious origin, long course and disfiguring disabling effects became one of the most dreaded of these conditions.

Born into the community, we inherit its social and religious ideas. In spite of the scientific evidence, ancient fears and prejudices regarding leprosy are extraordinarily ingrained and persistent, even in the most sophisticated societies. They invariably associate leprosy with ideas of guilt, rejection and isolation, so that even before he develops any symptoms the patient may be conditioned to anxiety by the very thought of leprosy, and the first suspicious symptoms may cause an acute emotional disturbance. I have encountered patients who burst into tears when told with the greatest discretion that they had leprosy, and equally others who burst into tears of relief when told they had no sign of it. The psychological trauma is thus there at the outset, conditioned by social attitudes and ideas. Its practical result is all too often the feeling that the disease must be concealed. For many a patient it requires no small amount of courage even to consult the doctor, and he comes fearing the worst.

2. *The stressful experience of leprosy*

The more one considers what it must feel like to suffer from leprosy, the more obvious is it that here is a disease which in its most common and ordinary manifestations is highly productive of psychological stress.

(a) *Facial lesions.* The frequency with which most of us look in a mirror is sufficient evidence of the importance society places on facial appearance. Facial

disfigurement, whether through unsightly patches, infiltration or paralysis is always an important source of anxiety, but there is one condition par excellence which experience has shown matters more than any other, and that is collapse of the nose, because this is thought to be pathognomonic of leprosy. In India patients often kept completely silent about their nasal symptoms because their anxiety regarding them was so acute, and only matched by their gratitude when the doctor showed his concern and initiated treatment.

(a) *Living with anaesthetic limbs.* The constant experience of numbness of the hands and feet, maybe for years on end, is inevitably stressful, while its attendant risks of burns and injuries must be a perpetual source of frustration and irritation. It is easy to tell the patient that his hands and feet are at risk, that he must inspect them daily, wear suitable footwear always, avoid handling hot cups, sharp instruments and so on. It is quite another thing for the average person to have his mind so concentrated on these things that he faithfully carries them out. Would we? For ordinary people lapses are inevitable in the demands of everyday life, with their equally inevitable results, but psychologically the cold insensitive hands and feet are themselves a sufficient cause of stress.

(c) *The impact of paralysis.* Paralysis of muscles occurs in other diseases. The peculiarly stressful element in leprosy arises from the selection of muscles involved, especially in the hands, and the manner in which this affects daily living. Loss of the capacity for delicate movements may have profound consequences where work is concerned. Equally profound is the effect on self respect when one becomes unable to wash oneself properly, do up buttons or tie the string of one's pants. These are common disabilities in leprosy.

(d) *Disturbances of sweating.* Loss of the capacity for sweating in one part of the body must be compensated for by increased sweating elsewhere. One of the common embarrassments of leprosy is the excessive sweating of face and trunk, and nothing can be done about this. At the same time, while hydrotherapy and oil massage may counteract the all too common dryness and tendency to cracking of the skin of the feet, here is another daily chore to make life burdensome.

(e) *Involvement of the genitalia.* This is very frequent in male patients with lepromatous leprosy, and a potent cause for the break-up of marital relationships. Even more than the nose, this is an aspect of his trouble about which the patient feels so strongly that he often does not mention it. Specific reference to it in the privacy of the consulting room often led patients in India to expose nodules on the scrotum or prepuce, with the opportunity for reassurance and comfort, occasionally backed up by minor surgery.

It is the cumulative effect of these various symptoms which gives leprosy its peculiar nature as a source of stress. When we add to them the eye complications, the reactive episodes, even the subtle odour which may accompany the disease when severe, we have here a situation unique in medicine.

3. *Stress in home and family life*

Yet a third area of stress arises from the destructive impact of the actual disease on home and family life.

One aspect of this is the threat of unemployment, always present as a result of social attitudes, but becoming really dangerous when work efficiency is impaired.

Within the family circle profound problems arise in relation to marriage. If the patient is a woman, in many societies she will be fortunate if her husband does not divorce her. If the patient is a young man engaged to be married, not only is his own marriage likely to be cancelled, but his unfortunate sisters may be

condemned to spinsterhood. The termination of sexual relationships between husband and wife is common in India, not only at the demand of the spouse, but frequently of the patient's own choice. It is widely believed that children are especially susceptible to leprosy, and acute anxiety regarding the children living in the house is almost commonplace.

Every patient who comes to us with leprosy, however early, is thus the target of stress from many angles. The result is all too commonly a depressive mental state. This is important, because it may affect the ability of a patient to respond in a normal responsible way to the advice of the leprologist, whether in relation to chemotherapy, hand and foot care, or cooperation in leprosy control measures. One encounters patients who regardless of the advice given, take in their anxiety one form of treatment after another, often in highly unsuitable dosage, and thereby provoke persistent reactive phases. In others, apathy leads to failure to take prescribed treatment, neglect of exercise, and loss of the will to recover.

Practical Measures

The first requirement in the response of the doctor is to see the patient in the light of his difficulties and receive him in a manner which convinces him that to us at any rate he is a person no different from other people. This involves courtesy, understanding and patience in all dealings with him, privacy in examination, the same levels of medical care as other patients expect from us. His cure begins with our acceptance of him as he is.

2. We shall offer him our professional skill, and there is no need for further reference to this. At the same time a positive attitude on our part to encourage his confidence and the sharing of his anxieties with us will certainly mean that he will return again and again and increasingly offer his cooperation and loyalty. At a leprosy hospital known to me, 70% of the numerous new patients come on the recommendation of old patients.

3. The sympathetic investigation of the patient's mode of life will often reveal contributory factors in persistent reactive phases and be of direct clinical importance. The alleviation of such factors may not be difficult and may lead to dramatic improvement also in his mental condition. A welfare or social worker is an essential member of the healing team.

4. The question of approach is particularly important in a leprosy control programme. It is not enough to provide facilities for DDS treatment somewhere within reach of the patient without going into the question as to whether he can actually avail himself of them. Control methods must be adapted to the actual situation of patients. As Kinnear Brown (1960) put it, "The outcome of the mass campaigns depends on the integrity, personality and assiduity of each individual participant, and on the confidence engendered in each patient that he is regarded and treated as an individual, and not just as another member of a milling crowd or an elongated weekly queue". The patient regularly taking DDS is a patriotic citizen and deserves to be treated as such.

5. Most important of all in the long term is the need for much greater emphasis on the leprosy education of the public as a deliberate policy. The facts do NOT speak for themselves. Only when continually re-iterated are they likely to have any impact on a conservative society, and produce that change of heart which alone will save the leprosy sufferer from his anxieties.

The Doctor Himself

Finally, what of ourselves in relation to leprosy, the doctor no less than his patients inherits the ideas of his community, and 6 years of medical training may not suffice to eradicate deep seated fears and prejudices. Visiting a young colleague at his clinic one day rather unexpectedly I found that it was his practice to sit at a table at one end of a large room with his register in front of him, while patients filed past at the other end of the room and received their DDS from a patient assistant. This was as near as he ever got to his patients, and there was no need to enquire further as to the cause of poor attendance and a general air of depression.

Success in leprology depends first on the doctor coming to terms with himself. We know that we and those who work with us are exposed more than most to infection with *Mycobacterium leprae.* We also know better than most the full range of facts about the transmission of *Myco. leprae* and can take appropriate precautions. Leprosy is surprisingly rare among workers at leprosy institutions. A positive lepromin reaction is reassuring. It can often be induced by repeated testing or by BCG. If confidence is still lacking, there is still the possibility of chemoprophylaxis. In the exceedingly unlikely event of the doctor catching the disease, the certainty of very early diagnosis and competent treatment with no lasting stigmata should suffice to rob both the disease and any fear of it of any sting.

The disappearance of secret fears and inhibitions opens for us a world of service to our patients, which for them means an available and reliable friend and adviser; and for the doctor the deep satisfaction of involvement in the battle against one of mankind's ancient and most intractable enemies.

Reference

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Lepr. Rev. (1976) **47**, 75-76

Letter to the Editor

Rifampicin in the Treatment of Reactions in Leprosy

The article of Steenbergen and Pfaltzgraff (*Lepr. Rev.* (1975) **46**, 115-118) provides evidence that rifampicin may aggravate Type I reactions and the drug therefore should be contraindicated in borderline-tuberculoid leprosy with neuropathy. The authors conclude: ". . . Type II reactions . . . do not seem to be at all exacerbated by the use of rifampicin, but rather to be somewhat suppressed." We wonder if such statements arise from an over-enthusiasm in the early days of a new and potent anti-leprosy drug. Waters *et al.*, (1967) warned: "Indeed nearly every effective new drug introduced for the treatment of leprosy has been claimed to give a lower incidence of ENL than does DDS. Subsequently these claims are usually abandoned."

The real influence of rifampicin on Type II reactions is not yet fully established. Leiker and Kamp (1970) found that 5 of their 7 patients developed reactions. In one patient, with BL leprosy, rifampicin had to be discontinued because of severe ulnar neuritis. Rees *et al.* (1970) mentioned that 2 out of 6 lepromatous patients developed ENL during a 4.5 months course of rifampicin. Of the 20 patients Wilkinson *et al.* (1972) described, one developed mild ENL; in another patient the drug had to be withdrawn because of a more serious Type II reaction.

Papers on rifampicin treatment were presented at the International Colloquium on the Chemotherapy of Leprosy, Borstel, 1974. If we tabulate the data of these rifampicin trials on lepromatous (LL and BL) patients, in which exact numbers of reactional states during therapy were given, the following results are obtained:

	No. patients	No. reactions	Reactions (%)	Mean treatment period
Rifampicin monotherapy	62	22	35	6 months
Rifampicin + Isoprodian	124	51	41	8.5 months
Rifampicin + other drugs	80	33	41	9 months
Total	266	106	40	8 months

There is no significant difference in the frequency of reactions between rifampicin monotherapy and rifampicin in combination with other drugs. However, the 9 patients who were recorded to have been withdrawn from their drug regimen because of severe reactions were all in the rifampicin + Isoprodian trials. Terencio de las Aguas (1975) found that his patients on rifampicin alone developed reactional episodes at a frequency of 0.08 per treatment month, whereas in the

group on rifampicin + Isoprodian this was 0.41 per month. On the other hand Gatti (1975) recognized more reactions during monotherapy than with combined therapy. An interesting paper was presented by Vomstein (1975) who studied the effect of rifampicin + Isoprodian on patients with initial reactions. Most of his 31 cases improved, although some remained thalidomide dependant. Three cases had to be withdrawn because of the intensity of their reactions.

We gave rifampicin (450-600 mg daily) to 4 male African LL patients *during* persistent Type II reactions. Three patients also received Isoprodian. In all 4 patients, although "covered" by prednisolone, the reactional state deteriorated. In fact their reaction with severe, sometimes necrotizing, ENL plus neuritis was so violent as to warrant stopping the newly introduced therapy. We had the impression that rifampicin in combination with Isoprodian gave more severe reactions than did rifampicin alone. Within 10 days of withdrawal the reactional episodes had subsided.

Type I reactions are believed to be a change in cell mediated immunity (Waters *et al.,* 1971). Rifampicin is reported to have suppressive properties on human lymphocytes stimulated *in vitro* with phytohaemagglutinin or PPD-tuberculin (Nilsson, 1971). Therefore one would assume that rifampicin could have a favourable effect on Type I reactions. The findings of Steenbergen *et al.* do not bear this out.

Type II reactions on the other hand are the clinical manifestation of an Arthus phenomenon (Waters *et al.,* 1971). Therefore rifampicin with its potent bactericidal capacities, releasing enormous quantities of free antigen, could have a deterimental influence on Type II reactions. This theory is supported by our findings, although our few cases are too limited for definite conclusions to be drawn. More controlled clinical studies are indicated to elucidate this problem. Until such trials have been completed, pronouncements on the favourable effect of rifampicin on Type II reactions should be considered with scepticism.

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Lepr. Rev. (1976) **47**, 77

Book Review

Guide to Leprosy and Leprosy Control, by Dr P. Kapoor. Published by Dr J. M. Mehta, President, Poona District Leprosy Committee.

Here is a book designed as a Leprosy Field Worker's Vade Mecum, and in this objective it succeeds admirably. Its primary target is the great body of para-medical workers within the National Leprosy Programme of the Government of India, but it will also appeal to busy medical practitioners who need something for ready reference when dealing with leprosy problems.

Dr Kapoor is a distinguished Indian leprologist with great experience of field workers and their problems. The book is written in synopsis style with clarity and brevity, and field workers will appreciate the tabular form in which points to be remembered are presented on almost every page. The subject is none the less dealt with comprehensively, with up to date emphasis on the practical aspects of leprology. Health education for instance occupies 5 of the 82 pages. With preventive physiotherapy so much the responsibility of the front line worker, a chapter on this subject, with simple diagrams, would have been welcomed.

The background is inevitably India and leprosy as seen in India, but para-medical workers everywhere and those involved in teaching them will read this book with interest and profit. For many it could be just the book to carry with them while on field duty. It is available in hard back and paper back editions, and we may hope that the need for another edition will give an opportunity to correct some printing errors. The price is not stated, but is certain to be very reasonable. The book is available from Dr J. M. Mehta, President, Poona District Leprosy Committee, 593/2, Rasta Peth, Poona -411 011, Maharashtra, India.

T. F. DAVEY

Lepr. Rev. (1976) **47**, 79-86

Abstracts

1. MICROBIOLOGY

1. SHEPARD, C. C., LEVY, L. & FASAL, P. **Further experience with the rapid bactericidal effect of rifampin on *Mycobacterium leprae*. *Am. J. Trop. Med. Hyg.*,** 1974, v. 23, No. 6, 1120-1124.

"The effect of rifampin therapy in leprosy was studied in two clinical short-term trials in which skin punch biopsy specimens were taken at regular intervals for the inoculation of mice in order to monitor the decrease in proportion of viable *Mycobacteriu leprae* in the patients' lesions. In a trial of rifampin in a dosage of 600 mg daily, the bacterial viability fell to undetectable levels in the first specimen taken after the start of therapy (at 3-4 days in 4 patients, 7-8 days in 9, and 14 days in 2). Dapsone-treated controls required 20 to more than 112 days for the same change. In a trial of a single dose of 1500 mg rifampin, the viability fell to undetectable levels in the first specimen taken after the start of therapy also (at 3-5 days in all 14 patients)."

2. NARAYANAN, K., MANIA, S., BEDI, B. M. S., KIRCHHEIMER, W. F. & BALASUBRAHMANYAN', M. **Experimental transmission of leprosy to animals: a preliminary note on attempt to transmit leprosy to the Indian pangolin *Manis crassicaudata* Geoffroy.** *Lepr. India,* 1974, v. 46, No. 3, 135-139.

The Indian pangolin has scaly armour and a low body temperature, and resembles the armadillo in some respects. Bacilli from a patient with lepromatous leprosy were inoculated into the animal; the result is to be reported separately.

C. S. Goodwin

3. DESIKAN, K. V. **Fate of *Myco. leprae* inoculated into foot-pads of mice.** *Lepr. India,* 1975, v. 47, No. 1, 9-14.

"During the first 3 months after inoculation of mice with *Myco. leprae* harvest of the footpads do not reveal any bacilli. The fate of bacilli during this period is not understood. Study has been conducted to assess the bacillary population in the footpads during this period. It has been found that the number of bacilli falls down to less than half the original number in 24 hours. After 72 hours, only 20% of the bacilli are recoverable. At the end of 8 weeks, harvest from the footpads are practically negative for acid fast bacilli. The possible causes of this steep fall are discussed."

2. IMMUNOLOGY AND PATHOLOGY

4. NAVALKAR, R. G., PATEL, P. J. & DALVI, R. R. **Immunological studies on leprosy: separation and evaluation of the antigens of *Mycobacterium leprae*. *J. Med. Microbiol.*,** 1975, v. 8, No. 2, 319-324.

"Chromatographically separated antigens of *Mycobacterium leprae* were tested for their ability to elicit skin reactions in guinea-pigs sensitized with homologous and heterologous mycobacteria. Of the 3 antigen-positive fractions obtained, one showed specific activity and the other 2 cross-reactivity, as indicated by studies of hypersensitivity and passive cutaneous anaphylaxis.

"The fraction exhibiting specificity contained only one antigen, which was protein in nature, whereas the other 2 fractions contained more than one antigen and possessed both protein and polysaccharide constituents. Because the single-antigen-containing fraction showed both positive skin and PCA reactivity, the suggestion is made that this fraction may contain either an antigen with 2 determinants or may contain 2 antigens that are not easily distinguishable by immunodiffusion methods."

C. S. Goodwin

5. McDOUGALL, A. C., REES, R. J. W., WEDDELL, A. G. M. & WAJDI KANAN, M. **The histopathology of lepromatous leprosy in the nose.** *J. Path.*, 1975, v. 115, No. 4, 215-226.

The recent revival of interest in nasal involvement in leprosy stems from a series of papers which have demonstrated the enormous output of bacilli from the nose that may occur in patients with the lepromatous form of the disease which is comparable to the output from an open case of tuberculosis. The present histopathological study is based on 151 nasal biopsies from 35 patients in Central India, all except 4 of whom had active lepromatous infections. Biopsies of 4 patients with borderline leprosy showed no signs of nasal involvement. In all the 31 patients with lepromatous leprosy, many acid-fast bacilli were found in at least one of the biopsy specimens, the bacilli always being associated with a cellular infiltrate but not with any particular anatomical site in the nose. They were frequently more numerous than in other parts of the body, with a higher percentage of solid (viable) forms than in skin. The main but not the only host cells were macrophages, though the infiltrate was pleomorphic. The number of organisms in blood vessels and lymphatics was striking; it was thought that the direction of movement of bacilli was from endothelial cells into lumen. Frequently these vessels were observed close to the surface epithelium and sometimes they had ruptured. Although there appeared to be various escape routes for bacilli, their discharge was due mainly to secondary infection in the presence of an expansile lepromatous infiltrate, together with simple trauma to the surface epithelium. This discharge is thought to be the main source for the epidemiological spread of *Mycobacterium leprae*. The paper is illustrated with 13 photomicrographs on 6 plates.

[See also *Trop. Dis. Bull.*, 1974, v. 71, abstrs 1028, 1999 and 2521; Rees and Ridley, *Bacteriology and pathology of leprosy*. In *Recent advances in clinical pathology*, Series Six, 1973, edited by S. C. Dyke, Churchill Livingstone.]

D. S. Ridley

6. CLOSS, O. ***In vitro* lymphocyte response to purified derivative, BCG, and *Mycobacterium leprae* in a population not exposed to leprosy.** *Infection & Immunity*, 1975, v. 11, No. 6, 1163-1169.

"Lymphocytes from 14 BCG-vaccinated donors, 7 tuberculin positive and 7 tuberculin negative by skin testing, were stimulated in vitro with 4 mycobacterial antigens, purified protein derivate (PPD), PPD/BCG, whole BCG bacilli, and whole *Mycobacterium leprae* and also with *Candida* antigen and phytohemagglutinin. The response was measured by incorporation of ^{3}H-labeled thymidine. The response to PPD, PPD/BCG, and BCG was found to correlate with the result of skin testing with tuberculin. The tuberculin-positive group also responded more strongly to *Myco. leprae*, whereas the 2 groups did not differ significantly in their response to *Candida* antigen or phytohemagglutinin. These findings indicate a certain degree of cross-reactivity between BCG and *Myco. leprae*. The use of the lymphocyte transformation test to measure antigenic cross-reactivity is discussed."

7. PAUL, R. C., STANFORD, J. L. & CARSWELL, J. W. **Multiple skin testing in leprosy.** *J. Hyg.* Cambridge, 1975, v. 75, No. 1, 57-68.

"Groups of patients with lepromatous and tuberculoid leprosy and hospital staff from 6 leprosaria in East Africa and 'non-contact' groups of villages or staff from general hospitals have been skin tested with 10 reagents. These were prepared by ultrasonic disintegration from *Myco. tuberculosis, Myco. duvalii, Myco. chelonei* and 7 other species identified in the Ugandan environment. Comparisons were made of the percentages of positive reactors in each study group for each reagent. The 'specific' defect of lepromatous patients was found to apply to a variable extent to 6 of the species tested, but not to *Myco. tuberculosis, Myco. avium* or *M. 'A*'*. The defect applied most noticeably to *Myco. nonchromogenicum* and *Myco. vaccae,* suggesting that they are more closely related to *M. leprae* than are the other species tested. The reagent Chelonin produced unexpected and anomalous results in the lepromatous group. It is suggested that this was due to an unusually slow clearing of Arthus' reaction."

W. H. Jopling

8. KWAPINSKI, J. B. G., BECHELLI, L. M., HADDAD, N. & SIMAO, E. T. **Impairment of reactivity to lepromin by mycobacterial antigens related to, or identical with, *Mycobacterium leprae.*** *Can J. Microbiol.,* 1975, v. 21, No. 6, 896-901.

"Three hundred and twenty young children were injected with Bacillus Calmette-Guérin (BCG) saline, or with one of the mycobacterial cytoplasmic antigens related with *Mycobacterium leprae.* At an appropriate time thereafter they were tested for dermal hypersensitivity to the antigens and for reactions to lepromin.

"Whereas all the antigens induced cell-mediated immunity, the incidence and intensity of late response to lepromin were significantly reduced in children preinjected with the cytoplasmic mycobacterial antigens, as contrasted with increased lepromin reactivity in the BCG group and with the findings in saline-injected children."

W. H. Jopling

9. BEIGUELMAN, B. & PISANI, R. C. B. **Effect of DDS on phytohemagglutinin-induced lymphocyte transformation.** *Int. J. Lepr.,* 1974, v. 42, No. 4, 412-415.

"The influence of DDS on PHA-induced lymphocyte transformation was investigated in leukocyte cultures from 2 samples of healthy Caucasoid individuals. In one sample the sulfone-treated cultures differed from the controls in that they contained 0.4 μg/ml of tissue culture medium plus PHA. In the other sample, the treated cultures contained DDS in concentrations of 4 μg/ml, 8 μg/ml and 16 μg/ml.

"The frequency of lymphocyte transformation induced by PHA was significantly reduced by DDS in all concentrations used. The data obtained are a strong indication that the plasma levels of dapsone among leprosy patients may contribute to the depression of the blastogenic capacity of their lymphocytes when stimulated by PHA."

W. H. Jopling

10 AZULAY, R. D. **Lepromin retesting as a factor of lepromin test positivation.** *Int. J. Lepr.,* 1974, v. 42, No. 4, 428-430.

"Repeated lepromin applications in guinea pigs induce a sensitization demonstrated by the progressive intensity of the reactions in subsequent tests.

"The peak of the lepromin reaction in guinea pigs is reached between 2 and 7 days, sooner than that which occurs in man (peak at 21 to 30 days). The lepromin reaction in guinea pigs is, therefore, shortened."

P. A. Jenkins

3. CLINICAL ASPECTS

11. IVESON, J. M. I., McDOUGALL, A. C., LEATHEM, A. J. & HARRIS, H. J. (1975). **Lepromatous leprosy presenting with polyarthritis, myositis, and immune-complex glomerulonephritis.** *Br. Med. J.* **3**, 619.

This is a case report on a Pakistani patient admitted to a general hospital in the UK with acute widespread polyarthritis accompanied with night sweats and fever. Reiter's disease and polyarteritis nodosa were excluded when as a result of muscle tenderness in the legs biopsies of striated muscle and skin revealed changes typical of lepromatous leprosy with large numbers of *Mycobacterium leprae.* Serum showed IgG-IgM cryoglobulinaemia without antiglobulin activity, and in the recovery phase renal biopsy showed a resolving proliferative glomerulonephritis with linear IgG and IgM immunofluorescence and granular deposits of C3. Clinical signs subsided rapidly under steroid treatment and subsequent progress on anti-leprosy drugs was uneventful. The term erythema nodosum leprosum is inadequate and misleading as a title for a common and important immune-complex reaction of lepromatous leprosy, in which numerous body systems may be involved.

From Authors' Summary

12. BARTON, R. P. E. **Lesions of the mouth, pharynx and larynx in lepromatous leprosy.** *Lepr. India,* 1974, v. 46, No. 3, 130-134.

In a study of the mouth, pharynx and larynx in patients with lepromatous leprosy, the author, working in Dichpalli, India, describes his observations. The cooling of these regions by the flow of inspired air is a significant factor in providing suitable conditions for the multiplication of *Mycobaterium leprae,* hence the involvement of the palate in patients who are mouth breathers because of nasal obstruction.

W. H. Jopling

13. GANAPATI, R. & DESIKAN, K. V. **Simultaneous occurrence of lesions of different types of leprosy in a patient—a case report.** *Lepr. India,* 1974, v. 46, No. 3, 148-151.

An Indian woman was admitted to the Central Leprosy Teaching and Research Institute, Chingleput, as a case of lepromatous leprosy, but detailed examination revealed a number of atypical skin lesions and thickened peripheral nerves. Histological studies showed lepromatous changes in nodules and borderline changes in atypical lesions, and the authors suggest that multiple biopsies in patients presenting with clinically dissimilar lesions would contribute to a better understanding of the immunological instability in borderline leprosy.

W. J. Jopling

14. SHESKIN, J. **The case for invisible leprosy.** *Int. J. Derm.,* 1975, v. 14, No. 5, 345-346.

The author briefly reports 3 instances of lepromatous leprosy diagnosed in Israel (out of a total of 262 patients known to be suffering from leprosy), in whom no recognizable and diagnosable skin lesions were said to have been present until, during an episode of erythema nodosum leprosum, lesions appeared that were typical and bacteriologically positive. [In such patients, tell-tale evidence of past leprosy, now quiescent, is almost invariably present in either the skin or the peripheral nerves or in both.]

S. G. Browne

4. THERAPY

15. PALANDE, D. D. **The ulnar nerve in the lower arm in dimorphous leprosy—some observations.** *Lepr. India,* 1974, v. 46, No. 3, 182-187.

This is a description of the findings in 38 leprosy patients at the Sacred Heart Hospital, Sakkottai, who required surgical exploration of one ulnar nerve because of intractable pain. External decompression was carried out in all cases and deep anterior transposition in some. There was no worsening of paralysis as a result of surgery and 17 patients experienced complete relief of pain.

W. H. Jopling

16. PATTYN, S. R. & SAERENS, E. J. **Minimal inhibitory dosage of rifampicin in intermittent treatment of *Mycobacterium leprae* infection in mice.** *Zentbl. Bakt. I. Orig., Ser. A,* 1975, v. 231, No. 4, 503-507.

"The total minimal inhibitory dose of rifampicin determined in the experimental mouse model, was found to be 10 mg/kg body weight, administered once a week for 6 weeks or once every 2 weeks for 12 weeks.

"From these and other results it is suggested that administration of RMP in human treatment can be reduced to a total amount of 7.2 g either as a 600 mg dose once a week for 12 weeks or as a 900 mg dose once a week for 8 weeks.

"At present these regimens can only be used as an introductory treatment for multi-bacillary cases and are still too expensive for developing countries, but their efficacy should be evaluated in the field as sole treatments in tuberculoid cases, since they could signify a substantial economy for the management of the majority of leprosy infections."

C. S. Goodwin

17, RODRIGUEZ, J. N., ABALOS, R. M., REICH, C. V. & TOLENTINO, J. G. **Effects of the administration of B663 [G30,320, Lamprene, clofazimine (Geigy)] on 3 groups of lepromatous and borderline cases of leprosy.** *Int. J. Lepr.,* 1974, v. 42, No. 3, 276-288.

47 leprosy patients in the Philippines were included in this trial, which was of 2 years duration. They were divided into 3 groups: group 1 consisted of 18 patients with relapsed lepromatous leprosy who were given clofazimine 200 mg/day for 6 days a week; group 2 consisted of 15 patients (8 lepromatous and 7 borderline) who were given clofazimine in similar dosage; group 3 consisted of 14 patients (7 lepromatous, 6 borderline, 1 indeterminate) who were given 100 mg dapsone daily for 6 days a week.

The reader will find it very difficult to gain a clear impression of the results of this study, but, if he makes a concentrated effort, will adduce that clinical response was satisfactory in all groups, but bacteriological and histological improvement was better in groups 1 and 2. Dark pigmentation of skin lesions was noted, but it was less marked in borderline lesions. With regard to erythema nodosum leprosum (ENL) reactions, clofazimine had a beneficial effect; whereas ENL was no problem in groups 1 and 2, it complicated treatment in 5 patients in group 3.

It is surprising that in assessing bacteriological improvement the authors report only on the bacteriological index and make no reference to morphology.]

W. H. Jopling

18. PEARSON, J. M. H., REES, R. J. W. & WATERS, M. F. R. **Sulphone resistance in leprosy. A review of one hundred proven clinical cases.** *Lancet,* 1975, July 12, 69-72.

"An account is given of the first 100 consecutive proven cases of sulphone resistance in leprosy, detected in Malaysia between 1963 and 1974. Proof of resistance was clinical in 80 patients and

was obtained by drug-sensitivity testing in mice in 96 patients; 76 cases were proved both clinically and experimentally, and there was no discrepancy between the 2 methods. Sulphone resistance was confined to patients with lepromatous-type leprosy—i.e., patients with a large bacterial population. Clinical evidence of relapse due to drug resistance appeared 5-24 years after the start of sulphone treatment. Low dosage favoured the appearance of resistance; therefore regular treatment of lepromatous leprosy with dapsone in full dosage is recommended. The attainment of 'skin smears negative for leprosy bacilli' is no test of cure of lepromatous leprosy."

W. H. Jopling

19. McLEOD, J. G. *et al.* **Nerve grafting in leprosy**. *Brain,* 1975, v. 98, Pt 2, 203-212.

The authors, writing from Australia, describe a nerve-grafting technique designed to correct sensory loss in leprosy. Median, ulnar, sciatic, and posterior tibial nerves were removed from cadavers within 24 hours of death and stored in physiological saline at 0-10° C for up to 2 weeks. They were then cut into suitable lengths and the diameters were measured. The nerves were freeze-dried, placed in individually sealed double-layered polythene bags and, after irradiation, stored at 4° C. Strips of infant dura mater were similarly prepared, and were subsequently fashioned into cylinders of varying lengths and diameters to be used as cuffs to hold nerve grafts in position. 23 nerve grafts were inserted into the peripheral nerves of 14 leprosy patients suffering from sensory loss: 10 into median nerves, 8 into posterior tibial nerves, 4 into ulnar nerves, and 1 was a branch graft from a median nerve proximally to both median and ulnar nerves distally. Azathioprine was given to each patient for immunosuppression. Results were good in 2 grafts, fair in 7 grafts, and poor in 8 grafts, 6 were failures. Although there was no return of motor function, no patient was worse clinically after operation than beforehand.

The authors consider these results encouraging but emphasize that the technique of nerve grafting in leprosy is only in the developmental stage and its limitation must be appreciated (See also *Lancet,* 1975, Aug. 2, 216.)

W. H. Jopling

20 NEBOUT, M. Bilan de huit ans d'autotraitement des lépreux du secteur no 3 de Moundou (Tchad). **[Results of 8 years' self-treatment of leprosy in the third sector of Moundou (Chad).]** *Bull. Soc. Path. Exot.,* 1974, v. 67, No. 5, 484-494. English summary.

The author writes enthusiastically—and convincingly— of the advantages of the scheme of self-treatment of leprosy introduced into certain countries of farancophone Africa. He describes the results of the first 8 years. functioning of the scheme in the country that pioneered it, the Republic of Chad.

Concurrently with the organization of the mobile teams supervising the out-patient leprosy treatment/control scheme, went the transformation of the oldstyle leprosy settlements into acute leprosy hospitals to which patients could be admitted for short-term treatment or investigation. Laboratory cover was ensured by a microscopist competent to examine the nasal mucus and skin biopsies.

By reducing the number of visits of the mobile teams, the cooperation of the local village leaders was enlisted and retained, a factor considered to be essential in the outworking of the programme.

The total number of patients under treatment fell from 17,071 to 6291 in 8 years, and the number "disease arrested" reached 10,364.

The prevalence fell from 3.7 to 0.83%, and the annual incidence from 0.12 to 0.011%.

The author attributes the success of the scheme to the complete coverage of the population, adequate provision for treatment, temporary hospitalization of those with multibacillary disease, the cooperation of the administration services, and health education of the population.

S. G. Browne

21. TOLENTINO, J. G., RODRIGUEZ, J. N. & ABALOS, R. M. **Controlled long-term therapy of leprosy with B663 (Lamprene, clofazimine) compared with DDS.** *Int. J. Lepr.,* 1974, v. 42, No. 4, 416-418.

This is a continuation of a preliminary report published in 1971 [*Trop. Dis. Bull.,* 1972, v. 69, abstr. 1685], and covers a 4-year period during which 16 of the original 43 patients completed the study, 9 on clofazimine (Lamprene; B663) and 7 on dapsone (DDS). The 2 drugs were found to be comparable in efficacy and safety, but erythema nodosum leprosum reactions were less severe and less frequent in the B663 group. No resistance to either drug was encountered.

[It is frustrating for the reader who wants to know about dosages used in this trial to be referred to the preliminary report.]

W. H. Jopling

5. EPIDEMIOLOGY, PREVENTION AND CONTROL

22. CHATTERJEE, B. R. **Are children the most susceptible to leprosy?** *Lepr. India,* 1974, v. 46, No. 3, 197-200.

In the area monitored by the Jhalda leprosy control unit in West Bengal the incidence of leprosy in children is 3 times lower than in adults. The incidence in children reported by other workers is reviewed.

C. S. Goodwin

23. SHARMA, S. N. & SAXENA, V. B. **An epidemiological study of rural leprosy problem in Dharsiwa block of Raipur district (M.P.).—I. Prevalence pattern.** *Lepr. India,* 1974, v. 46, No. 3, 157-171. **II. Transmission trends.** *Ibid.,* 172-181.

I. 8738 people, comprising 88% of the population, were examined for leprosy in a district of Madhya Pradesh; 38 cases of leprosy were discovered, a prevalence rate per 1000 of 4.34. 24% of the patients had lepromatous leprosy and 45% of the others had nerve involvement; "bilateral involvement was common". The prevalence in children was 26 per 1000. 9 tables give details of the survey.

II. Of 92 villages in which there were patients with leprosy, 38 had patients with lepromatous leprosy. 7 tables give analyses such as the age of onset of leprosy, history of leprosy in the family, result of lepromin test, and ABO blood groups.

C. S. Goodwin

6. REHABILITATION AND SOCIAL ASPECTS

24. DWIVEDI, M. P. **A study of medico social problems of cured leprosy cases in the Pandri village of Raipur District, M.P.** *Lepr. India,* 1974, v. 46, No. 4, 245-252.

Although this study was made 5 years ago in the State of Madhya Pradesh, India, it is unfortunately still relevant not only to other areas in the Indian subcontinent but also to South-East Asia, South America and Africa. The subjects were 132 families, comprising 286 people, living near a leprosy hospital. Altogether 222 of them, having had treatment for leprosy, were now regarded as "cured". They had been rejected by their relatives, denied a welcome and work by their fellow-villagers, and existed in single-person or small family units in a typical Indian village (like the "*villages de post-cure*" of francophone Africa).

At least three-quarters of them were classed as beggars; and only 15% were literate.

Addiction to hemp, tobacco and alcohol was very common, tobacco chewing being the principal addiction of the women.

Over half of the residents who had had leprosy retained some degree of disability—often severe, and usually stigmatizing.

The medico-social problems posed by this village of leprosy beggars, typical of many, are briefly and objectively described. The deep-seated social rejection of deformed leprosy sufferers, which leads to a feeling of apathy and inertia on their part, may be perpetuated by institutionalization and by unscientific and inhuman attitudes both to leprosy and to its victims.

S. G. Browne

25. RANNEY, D. A. **Rehabilitation goals in leprosy surgery.** *Lepr. India,* 1974, v. 46, No. 4, 253-257.

Writing out of his experiences in Karigiri, South India, the author summarizes the physical, socio-economic and psychological problems besetting patients suffering from leprosy. About a third of the patients had some degree of disability, due to neglected leprosy, already present when they first came for diagnosis and treatment— an indication of the inadequacy of case-finding procedures. Lagophthalmos resulting from upper facial palsy, claw hand and ulcerated feet point the obvious moral.

The author rightly insists on the importance of appearance as well as of function, if a patient with established deformity is to be accepted back into his family and community as a working member. Surgical correction or removal of obvious stigmatizing lesions is one of the ways to achieve this. Education in the use of insensitive extremities, retraining at one of the special centres available, the provision of tools and appliances with specially adapted handles may all help the ex-leprosy patient to face life anew and help the community to accept him.

Fear and rejection are the psychological factors that explain much of the meagre results accruing from many leprosy programmes. The patient with multiple deformities may need a succession of skilled surgical interventions before he is able to take his place in society.

[In the face of this rather grim picture of the difficulties encountered in attaining the goals enumerated, the modern insistence on prevention of deformity by early detection and adequate treatment assumes a greater importance.]

S. G. Browne

Thanks are due to the Director, Bureau of Hygiene and Tropical Diseases, for permission to reprint Abstracts from *Tropical Diseases Bulletin,* August-October 1975.

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The Physiology and Pathophysiology of the Skin

Volume 3

edited by A. Jarrett
Department of Dermatology, University College Hospital Medical School, London, England

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