Editorial

THE TREATMENT OF TUBERCULOSIS AND LEPROSY

The recently published ninth report of the WHO Expert Committee on Tuberculosis (1974) describes the very considerable advances that have been made during the past decade in the treatment of tuberculosis. It is timely therefore to consider some of the reasons why progress in the control of tuberculosis appears to be more rapid than that of leprosy, the nature of the areas where the most important advances in the treatment of tuberculosis are being made and their possible relevance to the treatment of leprosy.

Reasons for the relatively rapid advances in the treatment of tuberculosis

Many of the reasons for the more rapid advances that have been made in the treatment of tuberculosis are readily appreciated. A major factor has been the extensive screening of potential antituberculosis drugs *in vitro* and *in vivo* that has been carried out over the past 30 years in commercial as well as non-commercial laboratories. By contrast *Mycobacterium leprae* still cannot be cultivated *in vitro*, and the use of the mouse footpad model for screening potential antileprosy drugs *in vivo* is such a lengthy process that it has only been used by a small number of workers since its introduction 10 years ago, and apparently has not yet been commercially exploited.

Another major factor has been the numerous clinical trials that have been carried out during the past 20 years in Europe, North America and the Third World to establish the efficacy of alternative combinations of drugs in the treatment of pulmonary tuberculosis. Many of these have been meticulously controlled and in some of the trials the therapeutic responses of over a thousand patients have been assessed (East African/British Medical Research Council, 1974). These studies have been used to evaluate the influences of varying drug dosages and combinations, rhythms of drug admistration and durations of treatment on both therapeutic efficacy and toxicity (Fox, 1971*a*). By contrast far fewer controlled clinical trials have been mounted in the treatment of leprosy and most of them have been carried out on relatively small numbers of patients. Again, these differences are easy to understand.

The response to treatment of patients with bacteriologically confirmed pulmonary tuberculosis can readily be established. Thus patients are often considered to have responded favourably if tubercle bacilli can no longer be cultivated from their sputum during the last three months of a year of treatment. If treatment is then discontinued, normally only about 5% of such patients will subsequently relapse with active tuberculosis. Evidence can also be obtained by means of simple *in vitro* sensitivity tests as to whether patients failing to respond adequately to chemotherapy did so because of the inability of the drugs they took to kill a sufficient proportion of the initial population of drug-sensitive

bacilli, or whether it was on account of the drugs' failure to prevent the growth of drug-resistant mutants. The interpretation of the results of controlled clinical trials in tuberculosis has also been facilitated by the demonstration that the factor of overwhelming importance in determining the response of patients to treatment is simply the efficacy of the drugs they actually ingest during the treatment period (Fox, 1968; 1972).

By contrast it is still impossible to measure with precision the response of leprosy patients to treatment. Sufficient numbers of viable *Myco. leprae* for reliable bacteriological estimates of therapeutic response to be obtained are only present in lepromatous patients and it is only in such patients that the rate of elimination of viable leprosy bacilli is likely to be predominantly determined by the potency of chemotherapy. Treatment is also complicated by the occurence of *erythema nodosum leprosum* (Type 2 reactions) in lepromatous patients and reversal (Type 1) reactions in non-lepromatous patients.

Although the demonstration of a significant fall in the Morphological Index of a lepromatous patient indicates that the drug given has antileprosy activity, this method is normally only able to demonstrate whether during the period of treatment the population of viable *Myco. leprae* has been reduced to about 10% of its original number. Furthermore, because the process whereby dead leprosy bacilli become morphologically degenerate is relatively slow, this method inevitably grossly underestimates the rate of killing of *Myco. leprae* when a bactericidal drug is given. A subsequent rise in the Morphological Index despite continued treatment may suggest that the patient is relapsing on account of the appearance of drug-resistant *Myco. leprae*, but this can only be proved by subsequently demonstrating that inocula can multiply in the footpads of mice fed with doses of the drug that would normally prevent the growth of strains of *Myco. leprae* isolated from untreated patients.

Determining the length of treatment required before inocula from lepromatous patients become non-infectious for mice is a much more informative method of monitoring response to treatment. This method can be used to compare the relative bactericidal activity of different antileprosy drugs and is capable of following the reduction in numbers of viable *Myco. leprae* to about 1% of their original total. Although this method is fundamentally analagous to that used so successfully to assess the response of tuberculosis patients to treatment, it is much less sensitive and suffers from several very serious limitations. Firstly, because the numbers of viable leprosy bacilli have to be reduced to far less than 1% of their original total before there can be any reasonable hope of a "cure", it is unable to determine whether or not an adequate therapeutic response has been obtained. Thus while daily treatment with dapsone (DDS) for three months (Shepard *et al.*, 1972), or with rifampicin for as little as a week (Rees *et al.*, 1970; Shepard *et al.*, 1974) results in inocula from skin biopsies becoming non-infectious for mice, viable bacilli can still be isolated from other sites in the body after as many as 10 years continuous treatment with dapsone (Waters *et al.*, 1974) or after two years treatment with rifampicin (Rees, 1975), and would almost certainly result in the patients relapsing if treatment were stopped. Other major limitations to the method include the expertise required, its cost, and the many months that must elapse before conclusive evidence can be obtained that inoculated animals have become infected. As a consequence the method has been employed by few workers. Clearly much more sensitive methods are required to be able to detect far smaller proportions of viable *Myco. leprae* among inocula containing large

numbers of dead bacilli, if a satisfactory bacteriological definition of therapeutic response is to be obtained.

Relevance of the chemotherapy of tuberculosis to the treatment of leprosy

In view of the much greater wealth of knowledge concerning the treatment of tuberculosis, it is important to consider which findings may be particularly relevant to future advances in the treatment of leprosy. I believe there may be three such areas; firstly, the use of combinations of drugs to prevent patients relapsing because of the appearance of drug-resistant strains, secondly the use of supervised intermittent treatment to try to overcome the failures of chemotherapy caused by patients not taking their medicaments, and thirdly the importance of bactericidal drugs.

(1) The prevention of drug resistance

As Rees (1973) has pointed out, the introduction of dapsone for the treatment of leprosy preceeded the introduction of effective drugs for the treatment of pulmonary tuberculosis and the studies that demonstrated the necessity of giving combined chemotherapy to prevent tuberculosis patients relapsing through the appearance of drug-resistant strains of *Myco. tuberculosis*. Since treatment with dapsone alone appeared not to result in leprosy patients relapsing it is understandable that dapsone monotherapy became and has remained the standard antileprosy treatment. However the demonstration by the mouse footpad technique that a significant proportion of lepromatous patients ultimately relapse on account of the appearance of dapsone-resistant strains of *Myco. leprae* after many years of dapsone monotherapy, and the possibility that this may be a problem of increasing importance (Meade *et al.*, 1973), has suggested to several workers that the lessons gained from the treatment of tuberculosis should be applied to the management of lepromatous patients, and that such patients ought initially to be treated with combined chemotherapy (Pattyn, 1972; Shepard, 1972; Rees, 1973; Ellard, 1974; 1975*a*; Pearson *et al.*, 1975). The rationale for such an approach is the likelihood that less than 1 in 10^6 of the viable *Myco. leprae* present at the start of treatment will be naturally resistant to a given drug and that less than 1 in 10^{12} resistant to two drugs. Since the pretreatment population of viable *Myco. leprae* harboured by even the most florid lepromatous patient is unlikely to exceed 10^{11}, giving two effective antileprosy drugs ought to prevent the growth of all leprosy bacilli.

Controlled studies are urgently needed to investigate which companion drug would be most suitable for administering with dapsone, and the length of time for which it should be given before treatment can be successfully continued with dapsone alone. The most effective companion drug would almost certainly be rifampicin, but its extremely high cost severely limits how much can be given. The possibility of preventing the emergence of dapsone resistance in lepromatous patients by giving high dosage dapsone supplemented by an initial week of 600 mg rifampicin daily is discussed elsewhere (Ellard, 1975*a*). Long-term treatment with dapsone plus clofazimine (B.663) would probably be unacceptable to many patients because of skin discolouration. Other companion drugs that might be considered are thiambutosine (1500 mg daily) or thiacetazone (150 mg daily), although the adverse side-effects encountered with thiacetazone are such that one could not recommend its long-term use in several areas of the world (Miller *et al.*, 1970).

Controlled clinical trials in tuberculosis have also shown that if only a single drug (isoniazid) is used, its efficacy is improved if higher doses are given, due to the ability of such doses to suppress the multiplication of mutants with low degrees of resistance (Selkon *et al.*, 1964). Retrospective evidence from Malaya has also demonstrated that the incidence of dapsone resistance among lepromatous patients who were initially treated with sulphetrone is significantly higher than among those who were originally treated with dapsone (Mead *et al.*, 1973). Since the dapsone blood levels achieved by giving sulphetrone were considerably lower than when dapsone was given (Gelber *et al.*, 1974), there is therefore a strong case for treating lepromatous patients from the start with the highest doses of dapsone that are well tolerated (50-100 mg daily), whether or not a companion drug is also given (Pattyn, 1972; Rees, 1973; Waters and Helmy, 1974; Ellard, 1975*a*).

No case has been demonstrated of non-lepromatous patients relapsing through the appearance of drug-resistant bacilli, presumably because of the much smaller populations of *Myco. leprae* present pre-treatment and the greater immunological competence of the host. For these reasons monotherapy with dapsone remains the treatment of choice for non-lepromatous patients. Little additional therapeutic benefit would be expected by giving such patients high doses of dapsone. Indeed, in view of the widespread belief that the incidence of neuritis associated with reversal reactions in non-lepromatous patients is directly related to the dosage of dapsone employed, the accepted practice of treating such patients with more modest doses of dapsone (e.g. 25 mg/day) ought probably to be continued. Hopefully direct evidence concerning whether or not the incidence of such reactions is related to the dose of dapsone given will be obtained from a controlled study at present being carried out in Ethiopia (Personnal communication, R. St. Barnetson & J. M. H. Pearson). Further investigations in this area are to be encouraged since if it were true that the triggering of reversal reactions were directly related to the ability of treatment to prevent the multiplication of *Myco. leprae* it would be impossible to envisage a situation in which the risk of reaction could be minimized without the concomitant loss of all therapeutic benefits from treatment.

(2) Supervised intermittent chemotherapy

As Fox (1968*a*, 1972) has pointed out, the greatest threat to the success of even excellent regimens in the treatment of pulmonary tuberculosis is the difficulty of obtaining the long-term cooperation of the patient in the self-administration of oral medicaments for many months. The possibility of overcoming this problem by giving patients their drugs intermittently under full supervision was therefore investigated (Tuberculosis Chemotherapy Centre, Madras, 1963). A series of experimental studies were also undertaken at the Medical Research Council's Unit for Studies of Tuberculosis in London and at the Pasteur Institute in Paris to establish which antituberculosis drugs might be the most suitable for this purpose. These studies showed that drugs that were effective when given intermittently in the treatment of experimental tuberculosis in the mouse or guinea pig were those which were either capable of inducing prolonged bacteriostasis *in vitro* or possessed marked bactericidal activity. During the past 12 years a series of controlled clinical trials have demonstrated that twice-weekly supervised treatment can not only be highly therapeutically effective, but can also carry significant benefits in terms of lower toxicity and

cost (Fox, 1971*b*; WHO Expert Committee on Tuberculosis, 1974;; Ellard, 1975*b*). These clinical trials have also demonstrated the value of experimental studies in predicting the drugs that were most likely to be effective when given intermittently.

Inevitably the problem of leprosy out-patients failing to take the supplies of dapsone tablets that they have been given for self-administration is also of considerable importance. Thus Pettit and Rees (1964) showed that 4 out of 7 patients who had apparently failed to respond to sulphone treatment of over 13 years duration, promptly improved when their chemotherapy was fully supervised. More recently a study from Malawi has demonstrated that patients attending out-patients clinics had taken only about a half of their prescribed dapsone doses in the days immediately preceeding the clinic and that approximately 30% of the patients were grossly irregular in their drug taking (Ellard *et al.*, 1974). Similar findings have been reported from Ethiopia (Low and Pearson, 1974). Clearly, as Davey (1974) has pertinently commented, dapsone is not being taken by the numbers of patients intended, nor in the dosage expected, and although dapsone may be made freely available on the widest possible scale it does not follow that patients are going to take it in a way calculated to lead to the control of leprosy in the forseeable future. The irregular taking of dapsone may also be a major contributory factor to the development of dapsone resistance (Shepard *et al.*, 1969).

The efficacy of intermittent dapsone treatment is demonstrated by its ability when given once every week or fortnight to prevent the multiplication of *Myco. leprae* in the mouse footpad (Shepard, 1967*a*; Rees, 1967; Rees, cited Shepard, 1967*b*; Pattyn and Saerens, 1974), and the results obtained when lepromatous patients were treated in a controlled clinical trial with 50 mg dapsone twice-weekly (Pearson and Pettit, 1969). These findings suggest to the writer that the mass treatment of leprosy should be based on the daily self-administration of dapsone by out-patients *supplemented* by *fully supervised* intermittent dapsone administration. Thus lepromatous patients could be given 300 mg dapsone doses of dapsone to swallow under supervision at each visit to their out-patient clinic as well as a supply of 50 mg dapsone tablets for daily self-administration. Lower doses of dapsone (e.g. 25 mg) would be given to non-lepromatous patients for daily self-administration, together with larger supervised doses of dapsone *if* it could be shown by means of controlled studies that such doses did not significantly increase the risk of precipitating reversal reactions.

A major problem in the therapy of tuberculosis is that of patients ceasing to attend for treatment altogether. Such default probably reduces the total success of antituberculosis chemotherapy more than any other single factor (Fox, 1968*b*). The default of leprosy patients from treatment is also inevitably one of the most important factors hindering attempts at leprosy control in many parts of the world (Davey, 1974). Measures have been described for speeding up the visiting of defaulting tuberculosis patients (Fox, 1968*b*; WHO Expert Committee on Tuberculosis, 1974) that are equally applicable to leprosy patients. In this respect it is vital that clinics should be held as frequently as practicable. In many urban areas it should be possible to organize weekly clinics, while the use of mobile clinics in Malawi has demonstrated the feasability of organizing fortnightly clinics within reach of patients in rural areas. The practice of giving patients more than a month's supply of dapsone for self-administration should be strongly discouraged.

A further development that could greatly aid efforts to achieve and sustain effective levels of dapsone in leprosy patients stems from the demonstration by Shepard and his colleagues that continuously inhibitory dapsone levels can be maintained in patients by giving intramuscular injections of 225 mg acedapsone (DADDS), a slow-release form of dapsone, once every three months (Glazko *et al.*, 1968; Shepard *et al.*, 1968; Ozawa *et al.*, 1971; Russell *et al.*, 1973). The potentialities of using acedapsone in situations where medical resources are extremely scarce has been demonstrated in New Guinea by Russell *et al.* (1971). Several other workers have commented on the benefits that might be gained from the more widespread use of this remarkable drug, which is without parallel in the field of antituberculosis chemotherapy (Pattyn, 1972; Rees, 1973; Ellard, 1974; Pattyn and Saerens, 1974; Ellard, 1975*a*). Since acedapsone is well tolerated by all types of leprosy patients (Russell *et al.*, 1971; 1973), its use as an *additional supplement* for treating both lepromatous and non-lepromatous patients with oral dapsone regimens ought seriously to be considered.

(3) The importance of bactericidal drugs

Perhaps the most important recent advance in the chemotherapy of pulmonary tuberculosis has been the demonstration that certain regimens are capable of curing patients in as little as six months (Fox and Mitchison, 1975). Prior to this development treatment regimens have usually been of at least 12-24 months duration. A vital component of these "short-course" regimens appears to be the inclusion of at least two bactericidal drugs. Hopes that the introduction of the powerful bactericidal drug rifampicin might drastically reduce the length of treatment required to cure lepromatous patients have been dashed by the recent demonstration that viable *Myco. leprae* could still be recovered from certain selected sites after at least two years daily rifampicin treatment (Rees, 1975). It is tempting therefore to speculate about the possibility of curing lepromatous leprosy in a significantly shorter time if a second bactericidal drug could be discovered that could be used in combination with rifampicin and high dosage dapsone (Ellard, 1975*a*). Perhaps the most important characteristic required of such a second bactericidal drug would be the ability to kill the semi-dormant bacilli that appear insensitive to rifampicin's bactericidal action (Allen *et al.*, 1975, Fox and Mitchison, 1975, Rees, 1975).

However it must be admitted that speculation by itself is highly dangerous. All the major advances in the chemotherapy of tuberculosis resulted from extensive experimental studies and numerous controlled clinical trials. Similar advances in the treatment of leprosy can only be expected to result from much more extensive experimental investigations and the mounting of numerous large-scale controlled clinical trials. It is therefore of paramount importance than many more controlled clinical trials should be initiated, and that they should compare the efficacy of different alternative regimens in the treatment of many more patients and over a much greater period of time than has been the practice in the past.

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Neural Auto-Antibodies in Leprosy

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A new axonal antibody confined to peripheral nerve has been found at a significant titre of 1/30 by indirect immunofluorescence. This antibody occurred in 23 out of 59 sera from patients with lepromatous leprosy, 2 out of 10 sera from patients with tuberculoid leprosy from Malaysia and 1 out of 12 sera from patients with leprous neuropathy from Ethiopia, 4 out of 6 sera from patients with post-infective polyneuropathy and 6 out of 271 control sera.

Failure to remove the axonal antibody by absorption with BCG in six sera from patients with lepromatous leprosy and four sera from patients with post-infective polyneuropathy suggested that this was not a cross-reaction with *Myco. leprae* or other mycobacteria, but probably occurred as an epiphenomenon following nerve injury. The finding of axonal antibodies at a titre of 1/10 in 43 out of 271 control sera (15.8%) also suggests that the antibody's presence is not related to nerve damage. There were no antimyelin antibodies found in any of the sera studied.

Introduction

The presence of auto-antibodies in lepromatous leprosy has been widely investigated. Auto-antibodies have been found against testis (Wall and Wright, 1974), thyroid, nuclear material (Bonomo *et al.*, 1963) and cardiolipin (Ruge *et al.*, 1960), as well as rheumatoid factors and cryoglobulins (Matthews and Trautman, 1965). Antibody plays a part in the pathogenesis of erythema nodosum leprosum (ENL) and appears to cause tissue damage by immune complex formation (Wemambu *et al.*, 1969; Moran *et al.*, 1972).

Nerve involvement is found across the whole spectrum of leprosy (Ridley and Jopling, 1966; Pearson, 1972). In the tuberculoid form of the disease, nerve damage is associated with few leprosy bacilli and a granulomatous reaction

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(Pearson, 1972; Ridley, 1973) indicating an increase in cell mediated immunity. In contrast, in early lepromatous leprosy there is an insidious, continued loss of endoneurium associated with increasing numbers of *Mycobacterium leprae* in the surrounding Schwann cells (Ridley, 1973; Weddell *et al.*, 1964); at that stage little or no sensory loss may be detected, although at a later stage of the disease, progressive clinical neuropathy frequently occurs. In addition, especially in treated lepromatous patients, episodes of mononeuritis multiplex is a common feature of ENL. As it was considered that antibodies might play a role in producing lepromatous (but not tuberculoid) neuritis, the sera of lepromatous patients were investigated for the presence of antibodies capable of reacting with nerve tissue. For comparison, sera from patients with acute post-infective polyneuritis (Guillain-Barré syndrome) were also studied, as an immunological pathogenesis (Luijten *et al.*, 1972) has been suggested in this condition.

Sources of Sera

(1) LEPROSY

These studies were undertaken on leprosy patients from the Leprosy Research Unit at Sungei Buloh, Malaysia. Sera were examined from 59 adult patients, 50 males, aged from 14 to 71 (mean age 39 years, average age 35.5 years) and nine females, aged 21 to 48 (mean age 33 years, average age 32.7 years), suffering from bacilliferous leprosy; 56 were classified as lepromatous (LL) and three borderline lepromatous (BL) on the Ridley-Jopling spectrum (1966). Three patients were untreated, and six more also had active uncontrolled leprosy, three having relapsed through failure to continue on dapsone therapy and three having developed drug-resistant disease. The remaining 50 patients were all receiving effective treatment of varying duration. Forty-two had ENL at the time of entering the study, and three had had ENL in the past. None of the BL patients, and none of the untreated, or relapsed, off treatment LL patients had ENL. In 12 of the patients, a second sample of serum was obtained, 24 days to 15 months after the first. Some degree of peripheral nerve enlargement was detected in all patients, and evidence of motor and/or sensory nerve damage was found in the majority. Six patients were suffering from active ENL neuritis at the time of the taking of their blood specimen, and 21 more had either been diagnosed as suffering from ENL neuritis in the past or else developed the condition within 3 months of the time of study. Ten sera from patients with tuberculoid leprosy were also tested.

The patients were of Malay, Chinese, Indian or aboriginal origin, or a mixture of these races.

In addition, 12 sera were taken from patients with leprosy attending the MRC research unit, Addis Ababa, Ethiopia, in whom clinical nerve damage was present. The tuberculoid form was present in four of the patients, two were borderline and the remaining six patients had the lepromatous form, four with ENL.

(2) NERVOUS SYSTEM DISEASE

Sera from 33 adult patients under the care of the Neurological Department, Guy's Hospital, with a variety of nervous diseases (see Table 1) were studied. Nineteen were males and 14 females (mean age 37 years). The diagnosis of post-infective polyneuropathy was accepted only when there was a predominantly motor peripheral neuropathy following a minor upper respiratory or gastro-

intestinal infection, combined with cyto-albuminuric dissociation in the cerebrospinal fluid (Hinman and Magee, 1967).

(3) AUTO-IMMUNE DISEASE

This group consisted of 59 sera with auto-antibodies against nuclear material (24), gastric parietal cells (10), thyroid microsomal cells (10), reticulin (5), mitochondria (10); in addition four sera with high agglutinin titres against A and B blood group substances and two rabbit sera with antibodies experimentally raised against rat myelin (Gregson *et al.*, 1971) were studied.

(4) CONTROLS

Thirty eight sera from male Malaysian Chinese patients suffering from minor non-neurological conditions, 40 lyophilised sera from Ethiopian patients with relapsing fever, 40 sera from general hospital in-patients (Guy's) and 90 sera from English blood donors were studied as controls.

Methods

(1) IMMUNOFLUORESCENT TESTS

The unfixed and delipidated frozen rat tissue substrates used included transversely sectioned sciatic nerve with striated muscle, large intestine for myenteric nerve, and cerebellum. Unfixed guinea-pig peripheral nerve sections were also tested. Delipidation was carried out by soaking the 5 μm frozen section in warm acetone (28°C) for 2 min, followed by a series of "soaks" in warm ether (Lacey, 1972). In addition, frozen human testicular sections were treated with the lepromatous leprosy sera.

The indirect immunofluorescent test was carried out according to the WHO Manual of auto-immune serology (1969) except that it was not found necessary to inactivate sera at 56°C and the test was conducted at room temperature. Saline dilutions of positive sera at 1:10, 1:30 and doubling dilutions thereafter were tested to determine the antibody titre. A significant titre was taken as 1:30 (see Table 2). The following conjugates were used: sheep antipolyvalent human globulin conjugate (Wellcome Laboratories), specific sheep anti-human IgG, IgM and IgA conjugates (Wellcome Laboratories), rabbit anti-human β iC/βia conjugate (Behringwerke), anti-Fic conjugate (Hyland), and sheep anti-rabbit mixed immunoglobulin conjugate (Wellcome Laboratories). Results were recorded as negative, equivocal (±), positive or strongly positive. The microscope used was an "Ortholux" Leitz incident light microscope, with a quartz iodine light source for transmitted light and an HBO 50 lamp for incident light, a Turner interference filter 4950 AU (Gillett and Sibert) and an Ilford micro 4-blue gelatine secondary filter number 110. The incident light was used with a number three beam splitting dichroic mirror (TK 495) with two K 495 suppression filters in the turret. Both methods of illumination were used simultaneously.

(2) OTHER TESTS

The effect of absorption with BCG 0.2 mg moist weight, grown on the surface of Sauton's medium and twice washed, was investigated in 6 sera from patients with lepromatous leprosy and 4 sera from patients with post-infective poly-neuropathy. The efficacy of the process was assessed by testing the sera for

specific antibody before and after absorption, using immunoplates containing BCG antigen. Five sera from patients with lepromatous leprosy were absorbed with AB substance. Further absorption studies using sheet red blood cells were carried out on these sera. Immunoglobulin levels were determined in 20 sera from patients with lepromatous leprosy, using the radial diffusion method (Mancini *et al.*, 1965).

Results

Immunofluorescence was detected on the axons of the sciatic nerves of rats in 23 of the 59 sera from patients with lepromatous leprosy including 3 out of 3 with borderline leprosy from Malaysia, 2 out of the 10 patients with tuberculoid leprosy, and in 4 of the 6 sera from patients with acute post-infective polyneuropathy (Table 3). In most cases, the titre was low (1:30); the highest was 1:100. Only 6 out of the 271 sera from control cases tested (see Table 1) and one out of the 25 sera from patients with other neurological disease and drug peripheral neuropathy gave a positive axonal fluorescence. There was no statistical difference between the number of positives in the patients with neurological diseases, Malaysian control group, and the diverse control group ($P > 0.7\chi^2$ test). Two of the positive reactions in this group occurred in healthy adults, one from the blood donor group and one from a healthy patient with anti-nuclear factor present in his serum, while the other two positives occurred in the hospital in-patient group, one with coronary insufficiency and the other with disseminated lupus erythematosis. In the neurological control group, the positive test was found in a patient with neurosyphilis. In contrast, axonal staining was found only in one serum out of 12 tested, from patients (from Ethiopia) with nerve damage due to leprosy. There was no statistical difference in the incidence of axonal staining between this group and that of the non-leprosy relapsing fever Ethiopian control group and the diverse general controls (Table 3).

TABLE 1

Neurological diseases group

	Total
1. *Peripheral neuropathy*	
1. Post-infective neuritis persistent	5
2. Post-infective neuritis (resolved)	1
3. Vincristine neuropathy	1
4. Nitrofurantoin neuropathy	1
2. *Other Neurological diseases*	
Tabes	3
Meningovascular syphilis	1
Disseminated sclerosis	9
Cerebrovascular accident	4
Motor neurone disease	2
Epilepsy	3
Headaches	3
	33

TABLE 2

Distribution of "Axonal" staining in control series

Source	Positive 1/10	1/30	Total tested
Blood donors	6	1	90
General hospital in-patients	19	1	40
Relapsing fever (lyophilized), Ethiopian	5	0	40
Non-leprosy Malaysian-Chinese (in-patients) subjects	0	2	38
Autoantibody sera			
1. Antinuclear antibody	7	2	24
2. Gastric parietal antibody	1	0	10
3. Thyroid microsomal antibody	2	0	10
4. Reticulin antibody	1	0	5
5. Mitochondrial antibody	1	0	10
6. High titre agglutinins to AB blood groups	1	'0'	4
	43 (15.8%)	6 (2%)	271

TABLE 3

Distribution of "Axonal" staining at a serum dilution of 1/30

Source	Positive	Total
Lepromatous leprosy from Malaysia		
1. Active Neuritis present	5	6
2. Active Neuritis absent	18	53
Tuberculoid leprosy from Malaysia	2	10
Malaysian non-leprosy subjects	2	38
Leprosy with Neuritis from Ethiopia	1	12
Non-leprosy (relapsing fever) from Ethiopia	0	40
Acute post-infective polyneuritis	4	6
Other neurological diseases	1	29
Control series (see Table 2)	6	271

The presence of axonal staining in the sera from Malaysian lepromatous patients was highly significant when compared with sera from the control group ($P< 0.005\ \chi^2$), as was the presence of this reaction in sera from patients with acute post-infective polyneuropathy, bearing in mind the small number of observations, when compared either with the control group derived from the neurological department ($P< 0.005\ \chi^2$) or with the general control group ($P< 0.0005\ \chi^2$). The finding of the axonal antibody in 5 out of the 6 sera from patients with lepromatous leprosy and active ENL neuritis was suggestive of an association but did not quite reach a level of statistical significance, since the axonal antibody was also present in 18 of the sera from 53 lepromatous patients in whom no evidence of acute or subacute episodes of ENL neuritis was found ($P< 0.02\ \chi^2$).

There was no obvious association between ENL and the presence of axonal antibody, as the axonal fluorescence was detected in 17 out of the 45 patients

with present or past ENL and 6 out of 14 in whom ENL had never occurred. Of the 12 patients who had second specimens of sera tested, 5 were positive initially and negative when subsequently tested; however, 2 of the 7 patients who were initially negative were found to be positive when their second specimens were tested. In no patient was the immunofluorescent finding unchanged, perhaps indicating the transient nature of this reaction. The two patients without antibodies initially but who were positive on re-testing, were included in the positives referred to above.

There was no relationship between the presence of testicular antibodies and the axonal antibodies described above, since axonal antibodies were found in 17 out of the 52 leprosy sera with testicular antibodies and 6 of the 19 without ($P < 0.3\ \chi^2$). The prevalence of antinuclear factor using anti-IgG conjugates was low (2%) but with anti-IgM 37% of the sera were positive.

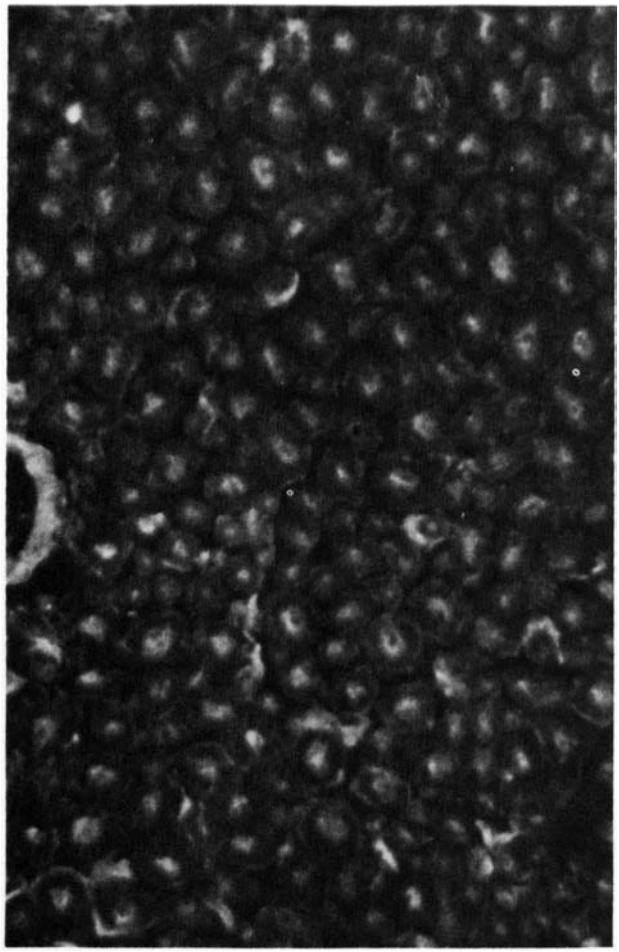

Fig. 1. Axonal fluorescence demonstrated by an anti-IgG fluorescent conjugate on rat sciatic nerve (acetone-ether fixed). (X 400.)

The immunofluorescent staining obtained with a proportion of the human sera tested was found on the sciatic nerve and was confined to the axon, staining it diffusely (Fig. 1). When nerve sections were cut longitudinally, the axonal staining appeared more filamentous than that produced by antimyelin antibodies. This immunofluorescence was not found on the axons of nerves in the cerebellum or those of the myenteric plexus. It is not definitely known whether this staining pattern was purely axonal or whether a component of myelin was also involved. Nevertheless, the participation of myelin is unlikely because in contrast, when sera containing guinea pig anti-rabbit myelin antibody was tested, the central core of the nerve fibre was left unstained but the myelin layer of the cerebellum (the medulla) fluoresced brightly. Denser axonal patterns were obtained in acetone-ether treated sections than in those left unfixed. The latter possessed the disadvantage that they gave patterns of staining which were blurred so that occasionally results were equivocal.

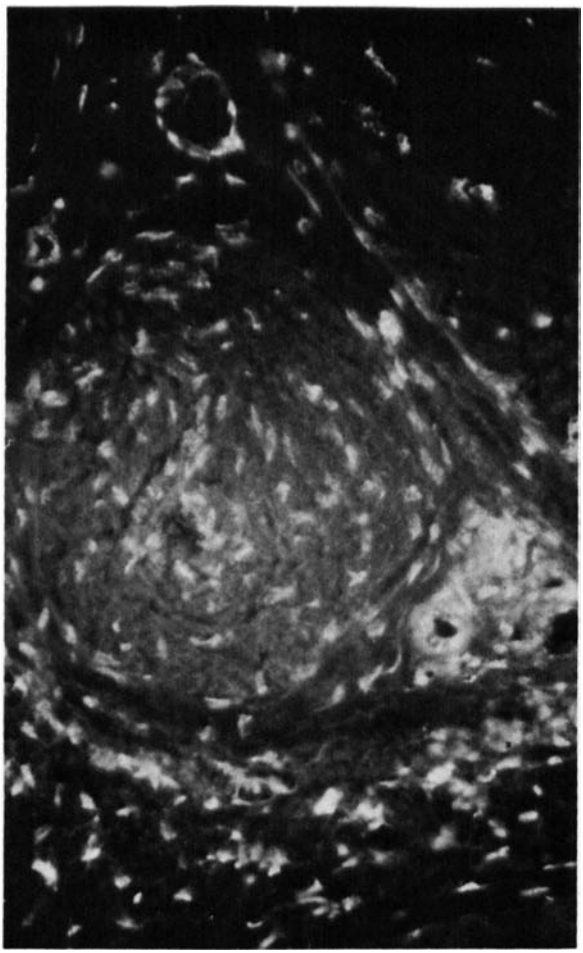

Fig. 2. Antinuclear factor staining nuclei of Schwann cells, as above. (X 250.)

The pattern of staining found on peripheral nerve was distinct from that obtained with antinuclear factor, which stained only the nuclei of the Schwann cells (Fig. 2). The presence of antinuclear factor in the appropriate sera was confirmed by observing that these picked out the nuclei of the granular layer of the cerebellum (Fig. 3), an appearance not to be confused with the cytoplasmic diffuse staining of the granular layer found with sera containing any of the mitochrondrial antibodies (Fig. 4). No consistent pattern of staining of peripheral nerve fibres was found when sections were treated with sera from any of the autoimmune disease control patients. (See Table 2.) Treatment of the nerve sections with anti-A and anti-B sera did not reproduce the staining pattern, nor could axonal fluorescence be inhibited by absorption of axonal positive sera with blood group substance; hence the fluorescence produced by leprosy sera was not due to anti-B blood group antibody. Sheep red cells were also ineffective in

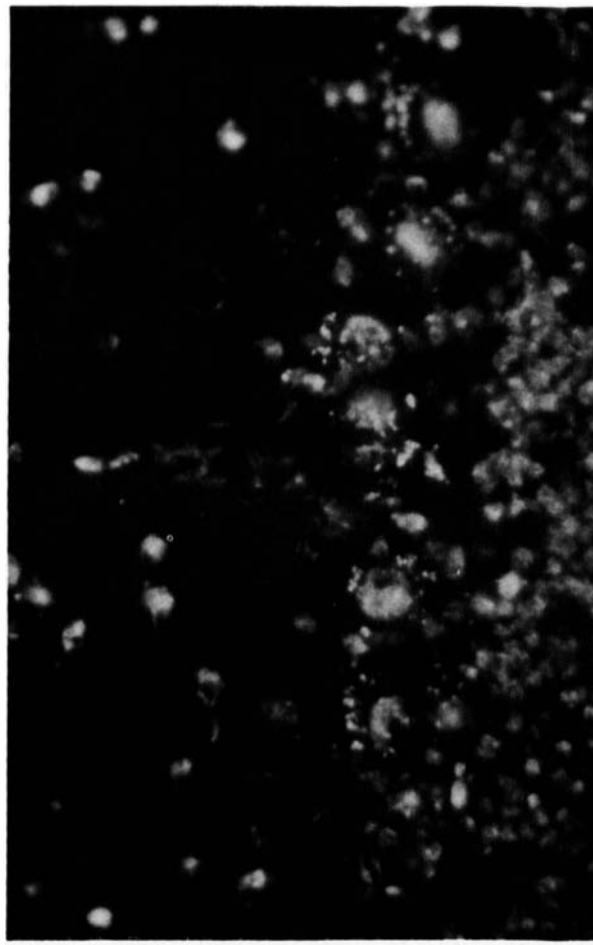

Fig. 3. Antinuclear factor staining the nuclei of granular layer of rat cerebellum. (Note staining of Purkinje cells), as above. (X 400.)

abolishing the axonal staining pattern indicating that this was not due to Forssmann-type antibodies.

Axonal fluorescence was restricted to the IgG class of immunoglobulin, since no staining was found when anti-IgM or anti-IgA conjugates were used. Fixation of complement was found in 4 out of 16 sera examined using anti-βic/βia conjugates. The immunofluorescent pattern was not abolished by repeated freezing and thawing or heating to 56°C. The staining pattern was not species-specific, identical fluorescence being found on rat and guinea-pig peripheral nerve substrates. The fluorescence was not due to non-specific absorption of circulating immunoglobulin, since there was no significant difference between the mean levels of IgG, IgM or IgA of sera with axonal antibodies and those without antibodies. The application of anti-Fic conjugate on the sciatic nerve sections did not result in axonal staining.

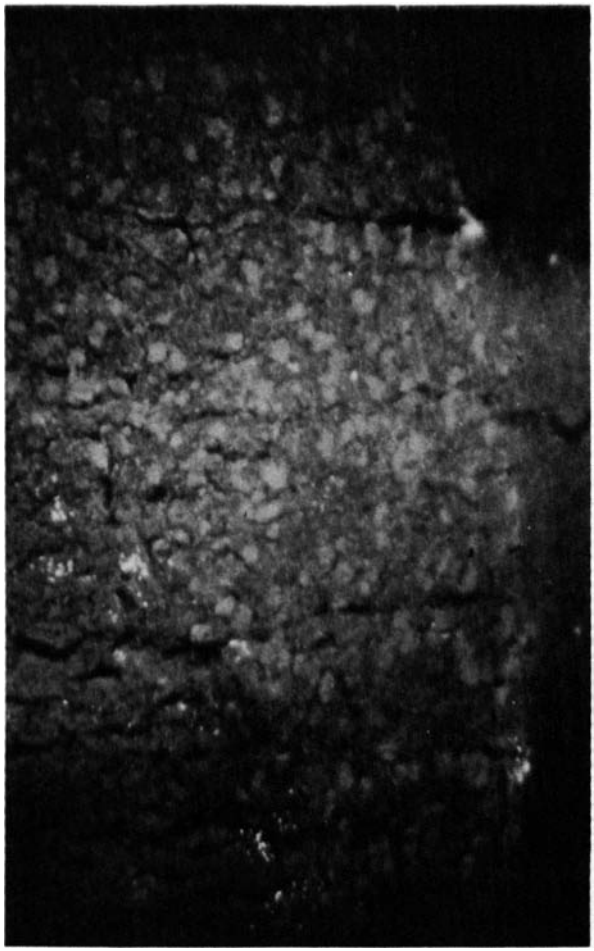

Fig. 4. Mitochondrial antibody staining the cytoplasms of the cells of the granular layer of rat cerebellum, as above. (X 250.)

When positive sera from patients with lepromatous leprosy or post-infective polyneuropathy were repeatedly absorbed with BCG, there was no resulting loss of axonal immunofluorescence or reduction in titre. This implied that the peripheral nerve pattern of staining was not restricted to leprosy or to mycobacterial disease, nor did the leprosy bacillus appear to be a specific inducer of this pattern.

Discussion

The selective binding of antibody to peripheral nerve axons has not been previously described. It is surprising that the axons of the nerves of the autonomic and central nervous system are not stained by this antibody, but this could be because of subtle antigenic differences in the molecular structure or denaturation products of peripheral nerve axon (Knowles *et al.*, 1969). It is possible that if tests were carried out on central nervous system tissue substrates using a serum containing antibody of high titre, axonal staining might be observed as clarity is sometimes difficult to achieve. There was certainly no correlation between the occurrence of axonal antibodies and antinuclear antibodies or anti-testicular antibodies, both present in leprosy (Wall and Wright, 1974). Reports in the past, using crude animal organ extracts, implied that there was a degree of immunological cross-reactivity between such disparate organs as testis and brain (Lewis, 1934), or thyroid and spinal chord (Beutner *et al.*, 1958). This has not been confirmed using more refined methods (Whittingham *et al.*, 1972). Similarly, the axolemmal staining described by Tomasi and Kornguth (1968) using an immunofluorescent method was quite distinct from axonal staining. Furthermore (their suggestion that axolemmal staining cross reacts with nuclei in the central nervous system was not confirmed) using anti-IgG conjugate in almost all our preparations.

The clinical association of axonal antibodies both with possibly post-infective neuropathy, a demyelinating condition, and with lepromatous leprosy, in which the site of the primary pathological change is not axonal but endoneurial, or in ENL, perineurial (Pearson, 1972), indicates that the pathogenesis is non-specific. The inability to absorb out fluorescence with mycobacteria provides further evidence that these antibodies may arise following injury to peripheral nerve. When nerve damage occurs in lepromatous leprosy, the Schwann cells and perhaps the perineurial cells release *Myco. leprae*, (Pearson, 1974; Weddell *et al.*, 1964) which may then lie either in close proximity to nerve axons or rarely in their interior (Boddingius, 1974). The unmasked axons combined with the adjuvant potential of the leprosy bacilli (Stewart-Tull and Davies, 1972) may provide a weak yet important antigenic stimulus for the production of axonal antibodies.

The detection of axonal antibodies in a proportion of leprosy patients in whom obvious progressive clinical neuropathy could not be detected suggests that sub-clinical nerve damage was occurring and further, that serial axonal antibody estimations may be helpful in the study of the incidence, natural history and treatment of nerve damage in these patients. The failure to relate axonal antibody to ENL is interesting, but must be taken with some reserve in view of the small number of lepromatous patients included in our series who had never suffered from this complication. The occasional positive reaction detected in our control series may also have been due to sub-clinical nerve damage, of uncertain aetiology. The virtual absence of axonal antibody from patients with leprosy neuropathy

from Ethiopia, may alternatively reflect racial variation in auto-antibody responses rather like that found with thyroid auto-antibodies in leprosy (Wright, 1973).

The finding of axonal antibodies is a rarity, whether in a Malaysian, European or Ethiopian population. Edgington and Dalissio (1970) did not detect any axonal staining in their normal control series, although they did report a high incidence of antimyelin antibodies, a finding which we could not confirm. A possible explanation is that they carried out their immunofluorescent tests using either neat sera or with sera in very low dilutions, just as, at a titre of 1/10, our control series sera more often showed axonal staining than at 1/30.

Allerand and Yahr (1964) could not demonstrate any affinity of immunoglobulin for normal central nervous system tissue, although this may not be true for the peripheral nerves (Abe, 1973). Furthermore, high levels of immunoglobulin, especially in such conditions as lepromatous leprosy (Bullock *et al.*, 1970), may well predispose to non-specific deposition of immunoglobulin on nerve fibres. However, direct measurements of the immunoglobulin levels were similar whether axonal staining was present or not. Thus the non-specific deposition of immunoglobulins on nerve fibres in leprosy is very unlikely, especially as sera from the majority of the patients who had ENL, the immune complex reaction of leprosy (Wemambu *et al.*, 1969), gave no neuronal immunofluorescent staining. Previously, the only instance of binding of immunoglobulin to human peripheral nerve was demonstrated by Luijten *et al.* (1972), who found that complement-binding IgM antibodies were deposited along the myelin sheaths of the autochthanous nerve fibres in four out of six cases of the Guillain-Barré syndrome, in which the dominant pathological change is demyelination. This finding could well have been due to the unmasking of axonal antigens following demyelination or perhaps related to axonal regeneration (McGuire and Grafstein, 1973) following injury, and similar mechanisms could explain the changes in lepromatous leprosy.

Like Diedreichsen and Pyndt (1968), we were unable to find anti-myelin antibodies or even any axonal staining with anti-IgM conjugates in the Guillain-Barré syndrome. This was surprising as myelin or myelin constituents, such as myelin basic protein, can evoke a humoral response especially in animal models such as allergic encephalitis (Mackay *et al.*, 1973; McFarland, 1970; Field *et al.*, 1963; Sherwin *et al.*, 1961) and experimental allergic neuritis (Winkler, 1965). However, this may bear no relation to the Guillain-Barré syndrome.

Furthermore, a defect in cell-mediated resistance is described in lepromatous leprosy (Dwyer *et al.*, 1973; Godal *et al.*, 1972; Rees and Waters, 1972). There is some evidence that auto-immune disorders may be associated with pathological processes in the thymus and that the immunological defect is due to a reduction in the level of thymic hormone. Reduced titres having been found in the auto-immune state in NZB mice. It has been suggested that thymic hormone prevents sensitisation to self-antigens, especially as normal adult lymphocytes have now been shown to have receptors for self-recognition (Trainin *et al.*, 1973). In this respect, the lack of inhibitor in leprosy described by Abe (1973) may be relevant.

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The Disposition of Sulfoxone and Solasulfone in Leprosy Patients

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Sulfoxone was administered to 14 patients and the levels of dapsone (DDS) and monoacetyldapsone (MADDS) in plasma and urine were determined by spectrophotofluorometric techniques. Peak plasma levels of DDS were approximately 600 ng/ml 5-8 h after treatment with 330 mg sulfoxone. The urinary excretion pattern of DDS and MADDS after this drug was similar to that found after DDS treatment, but total DDS excretion was lower. The results indicate that regular sulfoxone therapy provides plasma levels of DDS that would be expected to be therapeutically effective and to protect patients from the development of DDS-resistant leprosy.

A recently developed high pressure liquid chromatographic fluorometric procedure was used to determine plasma levels of DDS, MADDS and parent drug in six patients receiving solasulfone. After a single 500-mg intramuscular injection, plasma levels of DDS were only slightly above the minimal inhibitory concentration of DDS for *Mycobacterium leprae*, but the concentration increased 4-fold after six 500-mg twice-weekly doses. The rate of disappearance of solasulfone was rapid, but concurrent DDS and MADDS clearance times were longer than after DDS treatment. Direct relationships were found between 24-h DDS and solasulfone levels and among the disappearance rates of DDS, MADDS and solasulfone. Low levels of DDS after a single dose of solasulfone, as may be encountered in interrupted therapy, could be accompanied by an unusually high risk of the emergence or the selection of DDS-resistant *Myco. leprae* in certain patients.

Introduction

Earliest attempts to employ dapsone (DDS) therapeutically for treatment of leprosy patients were thwarted because it produced severe complications in the doses of 1 to 2 g thought necessary (Brownlee, 1950). To reduce the toxicity of DDS, several water-soluble derivatives (i.e., glucosulfone (glucosulfone sodium, Promin), sulfoxone (sulfoxone sodium, Diasone), and solasulfone (Sulphetrone)) were synthesized and were used extensively in leprosy therapy (Faget *et al.*, 1943; Lowe and Smith, 1949). Later studies (Smith, 1949*a*; Lowe, 1952) provided

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evidence that these compounds derived their activity from conversion to DDS. Concurrently, because therapeutic trials with lower doses of DDS in leprosy patients (Lowe, 1952) were successful with few complications, these water-soluble sulfones were discarded in favor of primary DDS therapy. Now, three decades later, several retrospective studies (Shepard *et al.*, 1969; Jacobson and Trautman, 1971; Levy *et al.*, 1972; Jacobson, 1973; Meade *et al.*, 1973) have indicated that resistance to DDS was a serious attendant complication to the use of these water-soluble sulfones.

The disposition of these water-soluble sulfones in man was determined earlier by applying the Bratton-Marshall procedure for measuring aromatic amines (Lowe, 1952). However, this technique possesses limited sensitivity and selectivity, and in many cases DDS levels could not be detected after treatment (Smith, 1949*b*). The need for measurements of greater sensitivity was emphasized by the finding that the minimal inhibitory concentration (MIC) of DDS was in the range of 2 to 10 ng/ml of plasma in mice or rats infected with *Mycobacterium leprae* (Ozawa *et al.*, 1971; Peters *et al.*, 1972*c*). Subsequent analytic developments for measuring small amounts of DDS in plasma (Ellard and Gammon, 1969; Peters *et al.*, 1970; Murray *et al.*., 1971; 1975) have made possible a realistic assessment of the DDS levels obtained in patients treated with these water-soluble sulfones. Now we can examine the suspected relationship between levels of DDS attained and the possible predisposition of patients receiving these drugs to DDS resistance.

In this study, we measured the levels of DDS and its major metabolite, monoacetyldapsone (MADDS), in the plasma of eight patients and in the urine of six patients receiving sulfoxone. Total DDS in the urine was also measured. In addition, we determined the disposition of DDS after three weeks of regular solasulfone therapy and contrasted these results with those obtained after a single treatment with solasulfone.

Methods

PATIENTS AND TREATMENTS

The participants in these studies were part of the patient population at the USPHS Hospital, Carville, La, U.S.A. They were fully informed of the purposes of the studies and participated voluntarily. The patients were divided into four groups. The composition of each was determined either by the drug received, the body fluid under study, or the treatment schedule. The patients ranged in age from 47 to 90 years and in body weight from 52 to 95 kg.

Sulfoxone (Abbott Laboratories, Chicago, Illinois, U.S.A.) was given as a single oral dose of 330 mg. Heparinized blood samples (10 ml) were taken at the times indicated in Table 1 from the first group receiving this drug. Plasma was immediately prepared and stored frozen. Urine was collected from the second group during 24 h following the same dose of sulfoxone (Table 1). The volumes of urine were measured and 50-ml aliquots were stored frozen.

The third group of patients received twice-weekly intramuscular injections of 500 mg of solasulfone (Burroughs, Wellcome and Co., Ltd., Bombay, India) for three weeks. Plasma samples were obtained after the sixth dose at the times shown in Table 2. To compare the results in patients on a regular schedule with those obtained from a single administration (as might be encountered in

interrupted therapy), we repeated the study in a fourth group whose members received only one injection of solasulfone (Table 3). All samples of plasma and urine were shipped via air on dry ice to the SRI laboratories for subsequent analysis.

In the past, chemotherapeutic treatment schedules of the two sulfone derivatives were: 330 mg oral sulfoxone, daily; or 500 mg intramuscular solasulfone twice weekly.

ASSAY PROCEDURES

Determinations of the possible influence of sulfoxone in the direct fluorometric procedure for measuring DDS and MADDS in plasma (Peters *et al.*, 1970) showed that 0.50 μg of sulfoxone (equivalent to 0.26 μg DDS, if hydrolyzed) contributed < 0.01 μg DDS. Because sulfoxone did not interfere in the assays for DDS and MADDS, this procedure was used to determine DDS and MADDS in plasma and in urine of patients receiving sulfoxone. Total DDS was also determined in urine after hydrolysis in 2 N HCl (100°C). Sulfoxone was hydrolyzed quantitatively to DDS by these conditions; therefore, the total DDS measured in urine would include the DDS conjugates known to be hydrolyzed to DDS (Peters *et al.*, 1970) and any unchanged sulfoxone.

Procedures previously employed to determine DDS and MADDS (Peters *et al.*, 1970; Murray *et al.*, 1971) were not applicable to assays of plasma from patients receiving solasulfone because this compound was rapidly hydrolyzed to DDS under the alkaline extraction conditions used in those methods. To avoid hydrolysis of solasulfone, we extracted plasma that was buffered to pH 7.4 as described below. Preliminary studies indicated that solasulfone in this buffer (0.6 to 1.0 mg/ml) was hydrolyzed to the extent of $< 0.2\%$/day (21°C) under these extraction conditions. Results of measurements of DDS and MADDS were the same (within 5%) in extracts of alkalinized or buffered plasma that did not contain solasulfone. Also, in some patients the levels of DDS and MADDS were found to be below the limits of sensitivity of our previously published procedures. Therefore, we employed recent modifications of a chromatographic-fluorometric technique for measuring DDS and MADDS (Murray *et al.*, 1975) that increased the sensitivity to 0.1 ng DDS or MADDS/ml of plasma.

To determine DDS and MADDS in plasma from patients receiving solasulfone, we added aliquots of plasma (0.50 ml) to 1.8-ml vials that contained 0.50 ml of 0.05 M KH_2PO_4-Na_2HPO_4, pH 7.4. Ethyl acetate (0.70 ml) was added and the vial was closed with a cap lined with a small piece of aluminium foil (1 × 1 cm). Extraction was carried out on an Eberbach shaker (Ann Arbor, Michigan, U.S.A.) for 10 min at 100 strokes/min. This slow shaking rate retarded formation of an emulsion. After centrifugation to separate the phases, DDS and MADDS in the ethyl acetate phase were determined fluorometrically after high pressure liquid chromatographic separation on a column of silica gel. DDS and MADDS calibration standards, solasulfone solutions, and reagent blanks were subjected to the same procedure. These assays revealed that the DDS content of the solasulfone preparation was 0.31%.

Because the recovery of solasulfone (as DDS) after mild alkaline hydrolysis of standard solutions was found to be nearly quantitative (94.1 ± 2.00%, mean ± S.E.), we employed this method to measure solasulfone in plasma. An aliquot of plasma (0.01 to 0.50 ml) was hydrolyzed in a solution that contained 0.50 ml of 1 N

NaOH, 0.02 ml of thiodiglycol (to prevent the degradation of DDS), and sufficient H_2O to adjust the final volume to 1.0 ml. The mixture was allowed to stand for 2 h at room temperature (21°C). Then the DDS formed was extracted into 0.70 ml of ethyl acetate and the extract was chromatographed as described. The recovery of solasulfone (as DDS) from standards in plasma was 82.0 ± 3.57% (mean ± S.E.). We have reported values obtained by this technique as "alkali-labile DDS" rather than as solasulfone because the procedure is indirect. For this reason, we have not corrected the experimental values for the lower than theoretical recovery from standards.

Previous investigators (Alexander *et al.*, 1970; Peters *et al.*, 1972*a*; Ellard *et al.*, 1974) concluded that after DDS treatment, plasma contained only DDS and MADDS and no other conjugates of DDS easily hydrolyzed to the parent drug. On the basis of these observations and the established susceptibility of solasulfone to mild alkaline hydrolysis, we have interpreted the very large increases of DDS found after this treatment of plasma from patients receiving solasulfone to be the administered drug.

The half-times of disappearance ($T½$) of the various compounds were calculated from the regression lines representing the logarithmic decay of their concentrations with time. Only those regression lines yielding correlation coefficients < -0.9000 were considered to yield valid $T½$ values. Differences between $T½$ values were determined by comparing the slopes of the regression lines.

Results and Discussion

SULFOXONE STUDIES

The upper part of Table 1 presents the mean levels of DDS and MADDS found in the patients at 4, 5.5, and 8 h following an oral dose of 330 mg sulfoxone. These values suggest relatively slow hydrolysis of sulfoxone, with peak levels of DDS and MADDS occurring between 5.5 and 8 h. These mean levels of DDS at the later times after sulfoxone are similar to the mean levels of DDS ranging from 560 to 680 ng/ml at 6 and 8 h that we found in Filipino and Indian subjects receiving 50 mg DDS orally (Peters *et al.*, 1974*a*; 1975). Because 330 mg sulfoxone contains 169 mg DDS (assuming complete hydrolysis to DDS), we can estimate that an approximately three-fold higher molar dose of sulfoxone than of DDS was required to yield similar plasma levels of DDS. Similar quantitative relationships were found in the blood levels of DDS in mice (Titus and Bernstein, 1949) and rabbits (Francis and Spinks, 1950) after administration of DDS and sulfoxone. These authors also reported that sulfoxone exhibited one-half to one-tenth the antibacterial activity of DDS when the two drugs were compared in equimolar doses. Regardless of the comparisons made above, it is clear that 330 mg sulfoxone given orally yields peak plasma levels of DDS that are substantially higher than the MIC of DDS for *Myco. leprae* (Ozawa *et al.*, 1971; Peters *et al.*, 1972*c*).

Our findings on the 24-h urinary excretion of DDS, MADDS and total DDS by six patients receiving 330 mg sulfoxone are summarized in the lower part of Table 1. Comparison of these mean values with corresponding percentages of a 100-mg dose of DDS (5.4% as DDS, 0.55% as MADDS and 31.1% as total DDS) excreted in 24 h by subjects studied earlier (Gelber *et al.*, 1971) indicates that the current patients excreted fractions of the dose as DDS and MADDS that were not

TABLE 1

Plasma levels and urinary excretion of DDS, MADDS and total DDS in patients receiving 330 mg sulfoxone orally

Hours after treatment[a]	DDS	MADDS	Total DDS
	Plasma level (ng/ml)		
4 (4)	305 ± 110.6	140 ± 59.0	—[b]
5.5 (5)	636 ± 175.8	218 ± 68.2	—[b]
8 (5)	656 ± 172.7	184 ± 50.4	—[b]
	Urinary excretion (% of dose)		
0-24 (6)	4.3 ± 1.34	0.34 ± 0.121	21 ± 4.9

[a] Values in parentheses are the number of patients studied. Other values in the table are the means ± standard errors of the mean.

[b] Not measured.

significantly different from those receiving DDS. However, less total DDS ($P < 0.05$) was excreted after sulfoxone than after DDS. The finding of less total DDS, even though the assay procedure measures unchanged sulfoxone as well as DDS conjugates, suggests that sulfoxone contributed very little, if at all, to the total DDS measured. Smith (1949*a*) also reported a large difference in the urinary excretion of total DDS during three days following oral sulfoxone and DDS by patients (53% versus 80%), and concluded that this was due primarily to relatively poor absorption of sulfoxone from the gastrointestinal tract.

Based on the plasma levels and urinary excretion of DDS after 330 mg sulfoxone treatment, it would seem that this dose is roughly equivalent to giving 50 mg DDS. One could anticipate, therefore, that such a dose of sulfoxone, taken regularly, would be adequate for therapy and would not be accompanied by unusual risk of the emergence or selection of DDS-resistant *Myco. leprae.*

SOLASULFONE STUDIES

As described in the Methods section, we found that the solasulfone preparation contained 0.31% DDS. Thus, the 500 mg of solasulfone administered contained 1.55 mg of DDS, and we would expect to find levels of DDS in the plasma at least reflective of that dose of DDS. The only pertinent data available on this point are from Ellard *et al.* (1971), who estimated a mean serum level of 18 ng DDS/ml in patients at 3 h after oral administration of 1 mg DDS.

Table 2 shows that 1 h after injection of solasulfone, DDS levels in three patients on scheduled therapy ranged from 46.6 to 142 ng/ml (mean, 80.7); the concurrent mean level of MADDS was 21.0 ng/ml (range, 3.5 to 40.5). Substantially higher levels of alkali-labile DDS (solasulfone) were found at this time. They ranged from 5910 to 11,000 ng/ml and averaged 8140 ng/ml. The mean DDS and MADDS levels increased moderately by the next blood sampling at 24 h (98.4 and 32.9 ng/ml, respectively) and thereafter declined slowly to the 72-h level. In contrast, the solasulfone levels decreased dramatically after 1 h. In these patients, the 24-h DDS and alkali-labile DDS levels were directly related

TABLE 2

Plasma levels and T½ values of DDS, MADDS and alkali-labile DDS in patients receiving multiple doses of 500 mg solasulfone intramuscularly

Patient No.	Hours after treatment	Plasma level (ng/ml)		
		DDS	MADDS	Alkali-labile DDS[a]
I	1	46.6	3.5	11,000
	24	60.7	10.6	2980
	48	56.8	9.3	814
	72	44.4	6.8	242
	T½ (h)[b]	106	75	13
II	24	177	28.7	4350
	48	167	26.4	1960
	72	143	21.4	940
	1[c]	142	19.1	7500
	72	110	16.7	1060
	T½ (h)[b]	156	113	22
III	1	53.4	40.5	5910
	24	57.6	59.5	2860
	48	52.2	56.0	1050
	72	46.0	44.0	420
	T½ (h)[b]	148	110	17

[a] These values were obtained after hydrolysis as described in the text.

[b] Values were calculated from the slopes of the regression lines obtained from plasma data at 24, 48 and 72 h ($r < -0.9$).

[c] This sample was collected 97 h after the previous dose.

($P < 0.05$), but no correlation was found between either of these two and the MADDS levels.

Also presented in Table 2 are the calculated T½ values for the three measured compounds in each patient. Solasulfone was cleared rapidly and the T½ values ranged from 13 to 22 h. On the other hand, both DDS and MADDS levels declined very slowly, yielding T½ values ranging from 75 to 156 h in the three patients. An apparent dependence of the T½ values for DDS and MADDS on the T½ of solasulfone was suggested by the finding that Patient II exhibited the longest T½ values for all three compounds with Patients III and I showing slightly lower T½ values in the same sequence.

The T½ values for DDS and MADDS in patients on multiple-dose therapy were substantially higher than the mean T½ values for these compounds of 28 to 31 h that we observed previously in African, Filipino or South Indian subjects or patients receiving DDS orally (Peters *et al.*, 1972*a*; 1972*b*; 1975). The longer T½ values of DDS and MADDS after solasulfone may have resulted from slow hydrolysis of solasulfone so that the circulation was continuously supplied with DDS. However, the rapid disappearance of solasulfone suggests that other factors must have contributed. One of these could be a relatively slow release of DDS formed from solasulfone at the site of administration. Thus, the multiple

administration of solasulfone may result in a partial repository effect. In this regard, we found previously (Peters *et al.*, 1974*b*) that DDS and MADDS are cleared very slowly from the circulation with *T½* values of 42 days following the intramuscular administration of 225 mg of acedapsone, the repository form of DDS. Also, other tissues may release DDS slowly following their saturation with DDS after the five or six doses of solasulfone. Recent studies in mice and rats fed diets containing DDS indicate that certain tissues exhibit levels of DDS and MADDS that are several times greater than plasma levels determined concurrently (Gordon *et al.*, 1974; Murray *et al.*, 1974). Whether these latter observations are applicable to patients receiving low doses of DDS regularly has yet to be determined.

The 24-h levels of DDS ranging from 57.6 to 177 ng/ml in the three patients receiving solasulfone are roughly comparable to the mean value of 800 ng DDS/ml at 24 h (Lowe, 1952) in patients receiving 3 g of solasulfone twice weekly by intramuscular injection, considering the six-fold difference in the doses. More recently, Gelber *et al.* (1974) reported DDS levels ranging from 60 to 120 ng/ml at 24 h after a single intramuscular injection of 1.5 g of solasulfone. These levels are similar to concentrations we found at 24 h after giving one-third of this dose twice weekly, emphasizing an apparent accumulation of DDS and MADDS with the multiple treatments.

TABLE 3

Plasma levels and T½ values of DDS, MADDS and alkali-labile DDS in patients receiving a single dose of 500 mg solasulfone intramuscularly

Patient No.	Hours after treatment	Plasma level (ng/ml)		
		DDS	MADDS	Alkali-labile DDS[a]
IV	0	<0.2	<0.3	<0.2
	24	17.2	14.7	2250
	48	18.6	16.5	817
	72	17.7	13.0	314
	T½ (h)[b]	–[c]	–[c]	17
V	0	<0.2	<0.3	<0.2
	24	16.5	5.5	1600
	48	6.9	1.8	394
	72	3.4	0.7	95.6
	T½ (h)[b]	21	16	12
VI	0	<0.2	<0.3	<0.2
	24	26.1	12.8	2940
	48	31.0	14.7	716
	72	31.1	16.0	211
	T½ (h)[b]	–[c]	–[c]	13

[a] These values were obtained after hydrolysis as described in the text.

[b] Values were calculated from the slopes of the regression lines obtained from plasma data at 24, 48 and 72 h ($r \leqslant -0.9$).

[c] *T½* was considered invalid because the *r* value was >-0.9.

From the levels of DDS found in these patients receiving regular twice-weekly injections of solasulfone, we would not anticipate an unusual risk of the emergence or selection of DDS-resistant *Myco. leprae.*

However, departure from this regular schedule may yield levels of DDS below the MIC for *Myco. leprae* resulting in poor therapeutic response. To test this possibility, we determined the levels of the three compounds in patients receiving only a single 500-mg dose of solasulfone. The levels of DDS, MADDS and solasulfone found are listed in Table 3. Mean DDS levels at 24, 48 and 72 h of 19.9, 18.8 and 17.4 ng/ml. respectively, were significantly lower ($P < 0.05$)* than the corresponding means in the group who received multiple doses over a three-week period. In Patients IV and VI, DDS did not decline after 24 h and, therefore, no valid $T½$ values could be calculated. However, in Patient V, the levels of all three compounds declined exponentially and $T½$ values of DDS and MADDS were found to be 21 and 16 h, respectively. This patient exhibited DDS levels at 48 and 72 h in the range of the MIC for DDS against *Myco. leprae,* and would be expected to exhibit a high potential for the emergence or selection of DDS-resistant *Myco. leprae* if not treated regularly.

Solasulfone levels in these patients were not markedly different from those receiving multiple doses. $T½$ values shown in the last column of this table were similar to those found in the previous group.

The lack of exponential decay of DDS plasma levels following a single dose of solasulfone was also apparent in the findings of Gelber *et al.* (1974). Using the plasma DDS levels reported by this group, we could not calculate valid ($r < -0.9$) $T½$ values for one-half of the eight patients they studied.

These investigations have shown that DDS levels adequate for chemotherapeutic activity are obtained during solasulfone treatment with 500 mg twice weekly. However, interrupted treatment, as exemplified by the studies after a single dose, could yield dangerously low levels of DDS in certain patients with the probable attendant potentiality of the emergence or selection of DDS-resistant *Myco. leprae.*

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Autopsy Findings in a Case of Lepromatous Leprosy Treated with Clofazimine

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The first recorded autopsy findings are presented on a young person suffering from intractable lepra reaction treated for four months with clofazimine in a dose of 300 mg daily. Apart from a generalized yellow colouration of fatty tissue, brick red in muscle and viscera, extreme congestion and oedema of the mucosa of the small intestine was found, and considered not to be caused by any infectious agent. Deposits of clofazimine crystals were found in the intestinal mucosa.

Introduction

Clofazimine (B 663) is now being extensively used in several leprosy clinics since its efficacy against leprosy as well as against lepra reaction has been well documented. (For review see Aguas, 1971). While its therapeutic action is generally satisfactory, the main side effect is the development of a violaceous colouration due to the accumulation of the rimino-phenazine dye in the skin and mucus membrane. It would be expected that in addition to the deposition in the skin and mucus membrane, the drug accumulates in the internal organs as well. This has been demonstrated in experimental animals (Conalty and Jackson, 1962) but there has been no record of similar changes in the human viscera in patients treated with clofazimine. We recently had an opportunity to examine the changes in various organs during post-mortem examination of a patient who had a course of treatment with B 663 prior to her death. To our knowledge this seems to be the first record of autopsy findings in a patient treated with B 663.

History and Clinical Features

The patient was a girl aged 12 years when she was first admitted in 1965 to the Central Leprosy Teaching and Research Institute, Chingleput, as a case of lepromatous leprosy. After about five months of treatment with DDS, she absconded from the Institute. Seven years later, she returned with the disease very much advanced and with severe lepra reaction. She was treated initially with antimalarials, and later with antimonial drugs, along with other remedies for relief of her symptoms. During this period, she had mild albuminuria with two to five pus cells per high power microscopic field. After about five months of medication

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with these drugs, the treatment was changed over to prednisolone, 15 mg twice daily. Examination of urine at that time revealed the presence of traces of albumin, pus cells and granular casts. Despite six weeks of treatment with prednisolone, the reaction continued unabated with the development of necrotising skin lesions. The patient was therefore put on 100 mg clofazimine three times a day along with prednisolone. She also received 1 mg DDS twice weekly. During this regimen the patient continued to have bouts of pustulating reaction, though of lesser severity, along with spells of diarrhoea. Examination of stools revealed plenty of pus cells. Clofazimine and prednisolone were continued and the patient also received antibiotics and antidiarrhoeal drugs. She continued to have a moderate albuminuria with pus cells and granular casts. Creatinine clearance was 69 ml/min, blood urea was 17 mg/100 ml. There was a marked reduction of plasma proteins. After about a month of treatment with clofazimine and prednisolone, she showed a significant improvement in her reactive state. In less than a week however, severe pustular reaction and lymphadenitis set in. She continued to receive clofazimine. The dose of prednisolone was increased to 40 mg a day along with antibiotics. She developed oedema of the face, chest wall and extremities although her urinary output was not seriously affected. The creatinine clearance was 57 ml/min. She continued to have bouts of diarrhoea necessitating reduction in the dosage of clofazimine and finally its total withdrawal. She had received clofazimine for a total period of nearly 4 months at 300 mg a day. One month later she died. The cause of her death was considered to be nephrotic syndrome, presumably precipitated by recurrent lepra reaction. Details of biochemical investigations carried out on a number of occasions are presented in the following table.

TABLE I

Biochemical findings

	27-7-72	24-8-72	22-9-72	18-10-72	4-11-72	22-22-72
Blood urea (mg/100 ml)	17	18	20	24	20	24
Serum protein						
Total g/100 ml		3.2	3.5	3.5	3.5	3.2
Albumin g/100 ml		1.5	1.8	1.8	1.6	1.5
Globulin g/100 ml		1.7	1.7	1.7	1.9	1.7
Serum cholesterol (mg/100 ml)		136	200	155	168	125
Creatinine Clearance ml/min	69	57				
Serum sodium (mEq/l)				136	134	130
Serum potassium (mEq/l)				4.0	4.3	3.0

Salient Post-Mortem Findings

The body was that of a moderately built adult female patient of lepromatous leprosy with extensive scars of healed ulcers all over the body. There was postmortem lividity camouflaging the colouration due to clofazimine. The

abdomen was distended and contained 3 l of clear watery fluid. The most striking finding on opening the abdomen and chest was the bright orange-yellow colouration of the fat and brick-red colouration of the muscles (Fig. 1). This colouration, particularly of the fat, was extensive throughout the body in all locations. The loops of intestine and the omentum were also found to be bright orange-yellow in colour, when the abdomen was opened. However, the colour faded on exposure to light for some time. The serosal surface of the intestine was smooth and there were no adhesions between the loops of intestine. On opening the small intestine, the mucosa was seen to be intensely red, extremely oedematous and markedly boggy (Fig. 2). A careful examination of the entire

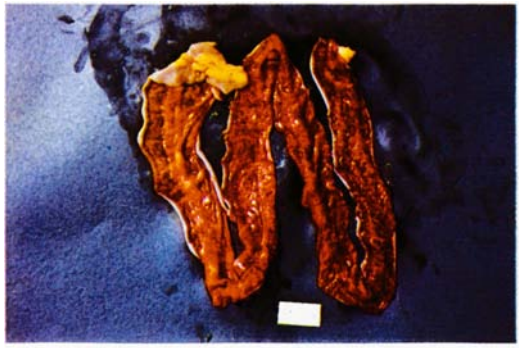

Fig. 1. Autopsy finding in the case treated with clofazimine. Note the bright orange-yellow colouration of the fat and brick-red colouration of the muscle.

Fig. 2. Mucosal surface of the small intestine showing the intense red colouration and oedema.

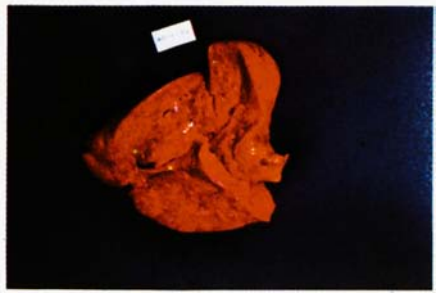

Fig. 3. Cut surface of the spleen. The bright brick-red colouration is quite distinct from the colour due to congestion of the pulp.

Fig. 4. Cut surface of the lung. Notice the bright brick-red colouration of the parenchyma.

length of the small intestine did not show any ulceration or necrosis. The large intestine was similar in appearance although not so severely inflamed.

The pleural cavities contained about 500 ml of clear watery fluid on each side. The right and left lung weighed 340 and 300 g respectively. The outer surface was smooth and bright red in colour. The cut surface showed bright brick-red colouration, which was quite distinct from the usual colouration due to congestion (Fig. 4). Both the lungs were well aerated. The larynx, treachea and bronchi showed no lesion.

The liver weighed 1500 g. The outer surface was reddish-brown in colour. The edges were rounded. The cut surface was congested and slightly greasy. The gall bladder and bile ducts showed no lesion. The pancreas was normal.

The spleen weighed 450 g. It was very firm and rubbery in consistency. The cut surface showed a prominent pulp which was bright brick red in colour (Fig. 3). The superficial lymph nodes were enlarged. The lymph nodes showed no significant lesion.

The kidneys were large, the right and the left weighing 140 and 160 g respectively. The outer surface was smooth. The capsule stripped easily. The cut surface showed the pelvic pad of fat coloured orange-yellow. The cortex and medulla were well demarcated. No significant lesion was seen. The ureters and bladder were normal.

The cardiovascular system and genital system showed no lesions. The brain and spinal cord were not examined. Of the endocrine glands, the thyroid, parathyroids and adrenals were examined. No macroscopic lesion was found.

Microscopic Findings

The most striking finding on gross examination was the extreme congestion and oedema of the mucosa of the small intestine. On histological examination the mucosa and submucosa were found to be infiltrated by polymorphs and lymphocytes. There was marked oedema with several dilated and congested blood vessels. There was no evidence of ulceration, necrosis or haemorrhage. A mild inflammatory cell exudate was also found in the muscular and serosal coats in areas. The large intestine also showed oedema and congestion of the mucosa with a moderate infiltration by polymorphs and lymphocytes. A search was made for clofazimine crystals. In the routine paraffin sections, these crystals were not found, apparently because during the process of preparing the tissue for paraffin sections and during staining, the crystals may have dissolved, leaving "ghosts" of the crystalline material. Such "ghosts" were found in the haematoxyline eosin sections, but their identity was doubtful. Frozen sections were therefore cut, mounted and examined, unstained. Careful search of these sections showed small collections of yellowish-black material in the intestinal mucosa. The location of these deposits and the shape of the crystals within the clumps are strongly in favour of the material being clofazimine crystals. The change in the colour of the crystals was thought to be due to the fixation of the tissues in formalin. Examination of fresh tissue material for clofazimine crystals was not carried out at the time of autopsy, and all the organs were preserved in formalin. Frozen sections of the formalin-fixed tissues were cut several days later, and this may have been the reason for the blackish colouration of the crystals in the sections. Apart from the intestine, the liver, spleen and lung also showed the crystals (Figs 5 and 6).

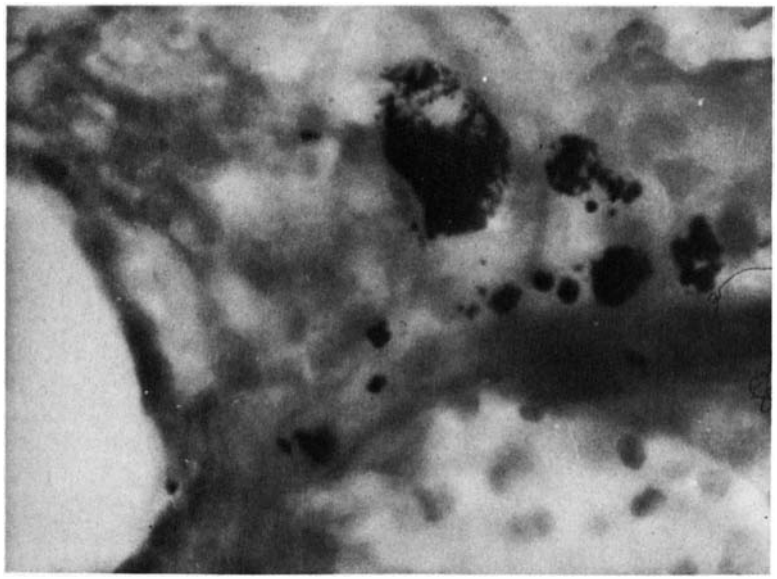

Fig. 5. Photomicrograph of the liver showing clofazimine crystals in a macrophage. (× 500.)

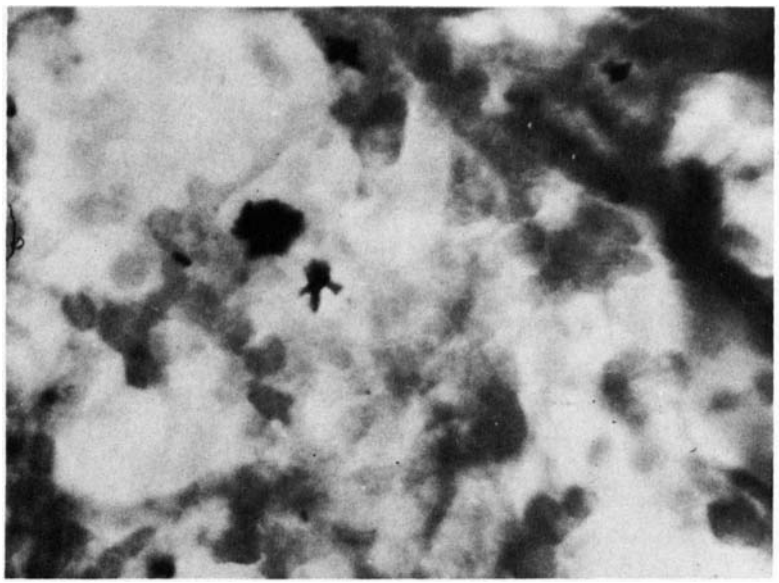

Fig. 6. Section of lung showing collection of the crystals in a macrophage. (× 500.)

Lepromatous granulomata, a millimeter or less in diameter, composed of collections of foamy macrophages with a few lymphocytes, were seen in the liver, occupying different parts of the lobule. Fragmented acid-fast bacilli in small groups were found in the macrophages. The bacilli were also found in small numbers in the Kupffer cells, and very occasionally in the liver cells. Miliary lepromatous granulomata containing acid-fast bacilli similar to those described above were also found in the spleen and in the adrenals. Lymph nodes showed partial replacement by lepromatous granuloma, mainly in the paracortical areas, and acid-fast bacilli were found in moderate number in the macrophage cells composing the granuloma. The larynx showed a lepromatous granuloma mainly in the vocal cords and epiglottis, with numerous acid-fast bacilli. The bacilli were also found in the bone marrow, kidney and lung, located mainly in endothelial cells of the blood vessels or in stray macrophages.

There was a massive amyloid deposit in the spleen. Most of the red pulp of the spleen was replaced by amyloid. The white pulp was seen as small islands of cells amidst the amyloid. A heavy amyloid deposit was also found in the kidney (Fig. 7). Most of the glomeruli were completely or partially replaced by the amyloid. The adrenal cortex was seen as a mass of amyloid material (Fig. 8). Small areas of zona glomerulosa were found intact, but the rest of the adrenal cortex was replaced by amyloid material. Amyloid deposit in the liver was very little. The blood vessels in practically all the organs showed amyloid change in varying degrees, marked particularly in the uterus and ovary. The organs examined showed no singificant lesion apart from the amyloid deposit in the blood vessel walls.

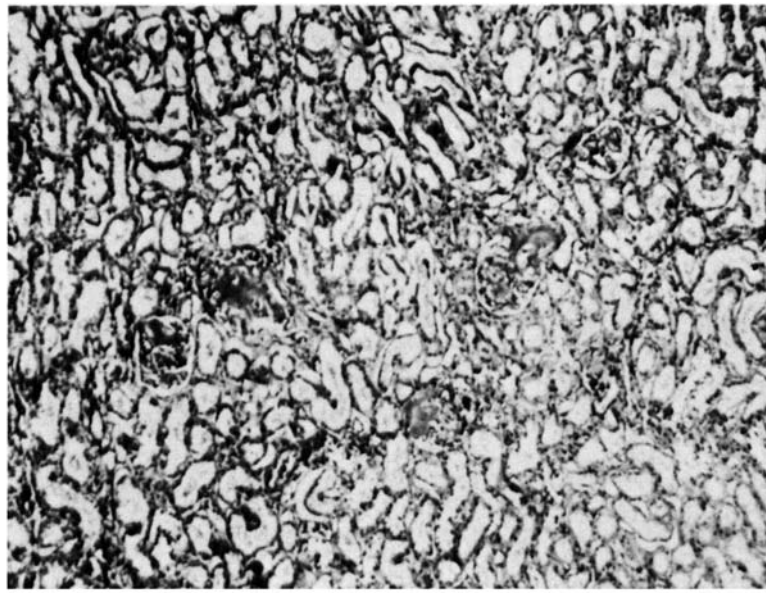

Fig. 7. Section of kidney showing amyloid deposit in the glomeruli. (H & E ×120.)

In summary, this 22 year old woman was a patient of lepromatous leprosy with repeated reactions. Having been treated with clofazimine, there was a striking colour change in the skin and internal organs. The subcutaneous fat, as well as fat in other locations were stained bright orange-yellow. Muscles, liver, spleen, kidneys and lungs showed bright brick-red colouration. The entire length of the intestines showed profuse oedema and severe congestion of the mucosa. Absence of ulcerations or necrosis indicated that this severe enteritis was not due to any infectious agent. Unstained frozen sections showed several small clumps of clofazimine deposited in the intestinal mucosa, lungs, liver and spleen. There was in addition a severe secondary amyloidosis, with massive deposit of amyloid in spleen, kidney and adrenal cortex and also an amyloid change in the blood vessels of organs. Lepromatous granulomata were seen in liver, spleen, lymph nodes, adrenal cortex and larynx. Acid-fast bacilli were seen in the granulomata as well as in the endothelial cells of blood vessels in other organs.

Renal amyloidosis was the cause of nephrotic syndrome in this patient. Some of the sequential biochemical observations carried out on various occasions showed a persistently low level of plasma proteins. There was albuminuria and a mild increase in the serum cholesterol level on one or two occasions. These features are consistent with nephrotic syndrome complicating lepromatous leprosy as has been reported earlier (Ramanujam *et al.*, 1973). However, she did not develop uraemia, but the sudden downhill turn of her condition and ultimate death could be explained by adrenal failure due to rapid amyloid deposit in the adrenal cortex.

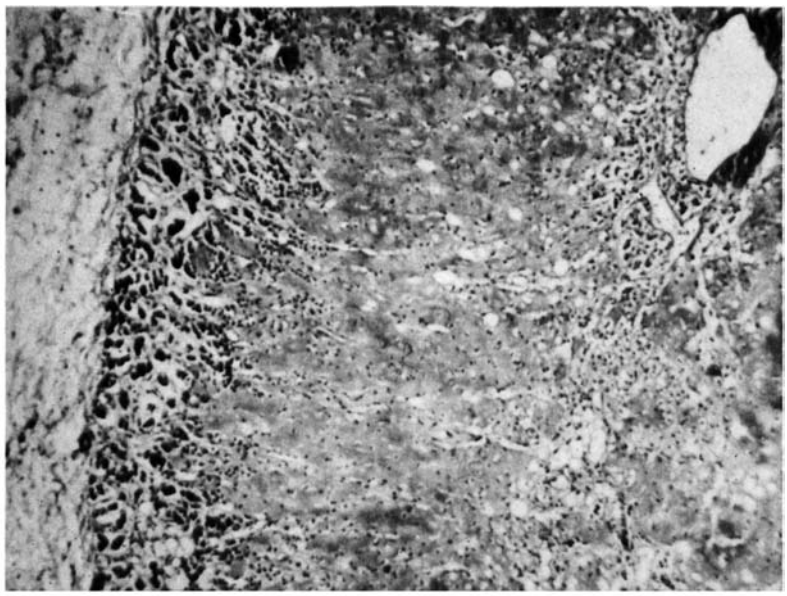

Fig. 8. Section of adrenal cortex with almost total replacement by amyloid. (H & E x120.)

Discussion

This case is being presented primarily to high-light the colour changes in the internal organs subsequent to clofazimine therapy. Although acclaimed to be a very efficacious drug against leprosy and lepra reactions, its chief disadvantage is the colouration of the skin, particularly in light coloured patients. Since the active ingredient of the drug is a dye which has a tendency to get accumulated in the RE cells (Conalty *et al.*, 1971) such a colouration of the organs is expected. Mice fed in this laboratory with diet containing 0.1% clofazimine showed colouration of the skin in the first week. After 4-6 weeks, it was found that the animals had lost considerable amount of weight. The subcutaneous fat showed bright yellowish orange colour. The liver, spleen and lymph nodes were reddish brown and the intestines were purplish black. These changes in animals have been described by other workers (Conalty and Jackson, 1962) but visceral changes in leprosy patients due to clofazimine therapy have not been reported. In the case presented, the colouration was most obvious in the adipose tissue in all locations. The subcutaneous fat, the fat in the omentum and mesentery was strikingly bright orange-yellow in colour. Such a colour change has also been observed in the subcutaneous fat while performing skin biopsies of several other patients on clofazimine therapy. Of the other internal organs the most striking colour change was found in the lungs and spleen.

One of the complicating conditions of the patient was the recurrent diarrhoea. A very careful examination of the intestine did not reveal any ulceration or necrosis. An infectious aetiology was therefore ruled out. The enteritis was in all likelihood due to clofazimine. Deposits of clofazimine crystals were found in the intestinal mucosa. It must be mentioned however that the reddish colouration of the mucosa was out of proportion to the comparatively moderate inflammation of the small intestine. This is obviously due to the staining by clofazimine which gave the startling impression of severe enteritis on gross examination. The diarrhoea in this patient was not severe and certainly did not contribute to her death, but it necessitated a reduction in the dose of the drug and its final withdrawal.

There have been several references in the literature to enteritis as a side effect of clofazimine therapy. Williams *et al.* (1965) described gastrointestinal disturbances in all the cases treated by them. One of the patients had abdominal cramps and severe diarrhoea necessitating frequent stoppage of the drug. These patients were receiving 600 mg of clofazimine daily. On a similar dose Atkinson *et al.* (1967) found that one of the patients had anorexia, epigastric distress, vomiting and abdominal pain with rebound tenderness. X-ray examination showed evidence of small bowel irritation. Peroral jejunal biopsy showed normal mucosal villous pattern with moderate number of plasma cells in the lamina propria. Devadasan (1970) has described abdominal discomfort in one patient out of eight treated. In three patients treated by Schulz (1972) with a maximal dose of 300 to 400 mg of clofazimine, there was constipation or diarrhoea severe enough to stop treatment. All routine examinations including roentgenography did not show any intestinal lesions. Two of these patients tolerated the drug in smaller doses. Ten other patients complained of transient abdominal pain and nausea, but the treatment with clofazimine was uninterrupted. Two out of 15 patients treated by Helmy *et al.* (1972) and one out of 20 patients treated by Pene *et al.* (1971) had abdominal discomfort, vomiting or diarrhoea, but treatment was uninterrupted.

Gastrointestinal disorders have also been mentioned by Aguas (1971) and Theophilus (1972).

Our own experience has been that gastrointestinal symptoms, especially diarrhoea, were a frequent side effect of clofazimine therapy, sometimes necessitating reduction of dose or temporary suspension of the drug. In the case presented, diarrhoea was frequent and severe. Consequently, the dose of the drug was reduced and finally stopped. It is interesting to note that although the patient did not have the drug for nearly a month before her death, and was practically free of diarrhoea, the morphological findings in the intestine were very severe, far more than was clinically obvious.

Acknowledgement

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Lepr. Rev. (1975) **46**, 191-194

Transverse Metatarsal Head Resection—A Radical Approach to the Problems of Forefoot Ulceration

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Transverse metatarsal head resection is recommended as a surgical approach to the problem of recurrent forefoot ulceration. This operation combines the soundness of a formal foot amputation with due consideration for the desires of patients. Indications and contra-indications are given, and the technique, described in detail, does not require sophisticated orthopaedic experience. The final results are extremely encouraging.

Ulceration of the forefoot is a common disability in leprosy patients. For many years it has been an established policy that such conditions should be treated as conservatively as possible.

Even with the best footwear and with the best care many of these patients return time and time again with fresh ulcerations. This is a heavy drain on the economy of the patient, and also on the hospital. There is an evident need for an approach to these problems that gives the patient a better chance of avoiding the disastrous results of recurrent ulceration.

Provided we are dealing with a foot with reasonably good plantar tissue in the mid- and hindfoot, and with reasonably good skeletal alignment of the tarsal region, a formal forefoot amputation is undoubtedly a sound approach. Performed with proper technique and on sound indications this approach reduces the incidence of re-ulceration considerably. The main objection to this is not so much surgical as psychological. Most of our patients are sentimentally quite attached to their toes, even though they may have been reduced to purely ornamental appendages. This we have to accept. *We* are not going to face life with obvious stigmata of leprosy.

This paper presents a surgical approach to this problem which combines the soundness of the formal forefoot amputation with due consideration for the desires of the patients.

The indications are that any kind of forefoot ulceration or of forefoot scarring poses a serious threat of frequent and progressive ulceration. Contraindications are ulceration and/or scarring of the mid- or hindfoot, since such conditions would not permit safe weightbearing on the reduced foot. Disorganisation and/or malalignment of the tarsal skeleton or the ankle joint are not, as such, contraindications. Such conditions usually require additional, drastic and sophisticated surgery. This, however, is outside the scope of this paper.

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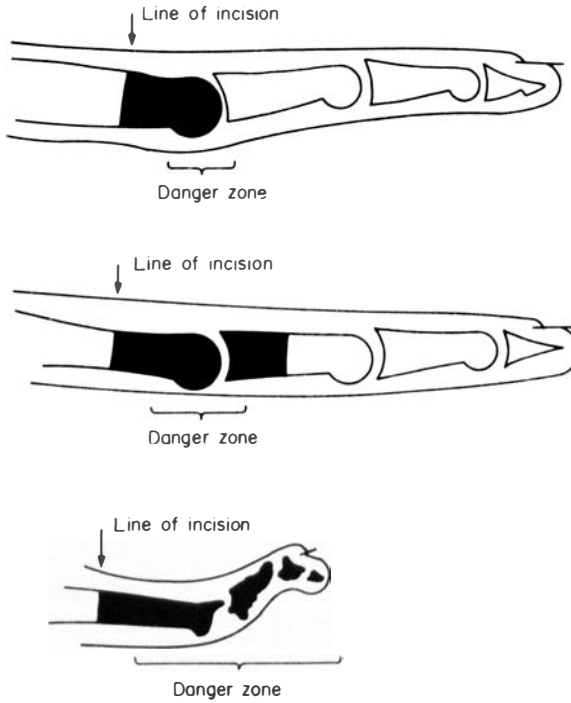

Fig. 1. Diagrammatic representation of the line of incision and of the amount of bone to be removed in three typical operations.

Proper surgical anaesthesia is necessary. Only if the operation is performed in a bloodless field can it be carried out in a satisfactory way.

The operation aims at removing sufficient amounts of skeleton from the forefoot so that the cut ends of the metatarsal bones are well proximal to the proximal edge of the ulcer/scar. This permits a troublefree take-off phase.

The incision is made transversely on the dorsum of the foot at the level of the proposed ostectomy of the metatarsal bones. It should be realised that this level is determined not by any considerations for the anatomy of the foot, but by the necessity of securing a sound take-off pad. The incision is carried down to the level of bone. No attempts at tendon repair are made. The metatarsal bones are divided subperiosteally in a straight transverse line. The distal portions of the bones are twisted out, including the metatarsal heads. Extreme care must be taken to remove any sesamoid bones, and also the occasionally found plate of more or less calcified/ossified osteoid tissue on the plantar surface of the metatarsal bones.

The resulting gap is loosely packed with plain vaseline gauze. The foot is dressed in a bulky dressing. This is left for 3-4 days, or even longer. After this period the foot is treated daily with soaks in plain soapy water and redressed as before. In the few cases where gross discharge of purulent matter or frank necrosis of tissue are found, eusol dressings help in clearing the wound. No indications are recognised for the local application of antibiotics.

This is essentially the regime advocated by the past masters of treatment of osteomyelitis, Trueta, Orr and Chiewitz. The classical instructions call for untouched bandages "until the nurses faint". The recommended technique may not be better, but it does leave the air in the ward fresher and more pleasant.

Soon the cavity starts contracting and granulation tissue appears. Eventually a thin, linear scar is left on the dorsum of the foot. The ulcerated or scarred plantar tissue has been relieved of its adhesions to the skeleton and is allowed to retract. In practically all cases the end result is that the thin, adherent, ulcerprone plantar tissue is replaced by a quite respectable plantar pad.

One variation of this technique calls for removal of the metatarso-phalangeal joints, occasionally even the whole of the proximal phalanges. Usually this is indicated where septic arthritis is a feature, or if simple resection of metatarsal heads and necks does not produce a sufficiently wide gap in the skeleton.

In another variation the distal portions of the metatarsal bones are removed, and all the remnants of bone that are found distal to the former metatarso-phalangeal joints are removed. This is frequently indicated where we are dealing with the type of absorbed forefoot, that externally looks rather like a forefoot amputation, but has a very thin, adherent plantar tissue in the take-off area. Wherever indicated this procedure can easily be supplemented by resection of one or more of the proximal interphalangeal joints. It has been found satisfactory to perform the resection exclusively of the fourth and fifth, or of the fifth metatarsal bone, but otherwise following the described technique. This demands good plantar tissue in the remaining forefoot.

A similar approach to the first metatarsal bone is possible, but the results are less satisfactory. The postoperative gait is frequently disturbed.

Isolated metatarsal head resection of one or more of the central metatarsal bones is contraindicated. It does not permit sufficient retraction of the plantar tissue to produce a serviceable plantar pad.

A description of the indications and contraindications for metatarsectomy, removal of one of more metatarsal bones *in toto,* is outside the scope of this paper. Generally speaking we have found that a short, broad foot—other conditions being equal—is more serviceable and has a higher resistance to re-ulceration than a long, narrow foot.

There are few complications. Very occasionally post-operative bleeding causes anxiety. Proper dressing and properly applied compression bandage, combined with elevation of the operated foot is sufficient to control this. The blood supply to the distal flap may very rarely be insufficient. The result is necrosis of parts of the distal flap. During the 1½ years this operation has been in regular use in this unit, this has only happened twice. In both cases the end result was a very nice and pleasing forefoot amputation. Pockets of pus may be found tracking proximally in the depths of the foot. They should of course be properly drained, but do not otherwise change the technique or influence the results. Antibiotics are extremely rarely indicated. It is sounder and safer to rely on good surgery rather than on antibiotics.

The final results are extremely encouraging. The dorsal scar usually presents no difficulties. Only occasionally may a deep scar call for secondary plastic revision. The forefoot assumes a normal alignment. The plantar tissue in the ulcer/scar area somehow remodels as a perfectly serviceable take-off pad. We have had only two cases of re-ulceration. In one case a young girl returned with a huge nail perforating the sole of her shoe. In the other case an adult man returned, rather

shamefaced, to report that he had overlooked a sharp stone in the shoe. In neither case did the re-ulceration occur in the take-off area of the shortened foot.

All have been fitted with protective sandals of the type that routinely are issued to patients with anaesthetic feet. Only if more extensive surgery of the tarsal skeleton has been performed, has more sophisticated footwear been indicated.

In the early days there was a quite understandable reluctance to accept such mutilating surgery. Gradually, as the results became known, the "hidden amputation" as it is known locally, has gained in popularity. It has been interesting to notice that several patients have realised the indications and have requested this operation.

The required instruments, a scalpel, a tissue forceps, a couple of rongeur forceps and a periosteal elevator, are certainly within the reach of any leprosy hospital. The indications and contraindications are clear and do not require sophisticated orthopaedic experience. The technique is simple enough for any physician with some interest in surgery to learn to perform it competently. The results are encouraging enough to warrant use of time, bedspace and money.

Lepr. Rev. (1975) **46**, 195-198

The Accurate Measurement and Recording of Plantar Ulcers

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A method is described for the accurate recording and measuring of plantar ulcers which may easily and effortlessly be introduced in the routine management of such ulcers. Applications are discussed. It is hoped that the use of this or similar methods may help throw more light on factors involved in the healing process, help compare and evaluate treatments available and above all help the clinician in the management of the patients in his care.

Introduction

Ulceration of the anaesthetic extremity is one of the major causes of bed-occupancy in leprosy units. It is also one of the complications most frequently met with in out-patient clinics. Above all it is for the sufferer from leprosy a cause of much morbidity, stigmatisation and, all too often, the cause of permanent deformity and disability.

Our priority must lie with preventive measures designed to reduce the number of ulcers occurring, but it is also of great importance that we should heal those ulcers which do occur as quickly as possible in order that the patient may be quickly restored to his place in the community – and liberate precious beds. It may be that we should therefore devote more attention towards those factors involved in ulcer healing and to evaluating methods available for treatment. A quick and accurate method of serial mensuration of ulcers, with consequently the possibility of attaching statistical values to their rates of healing, may help in this respect. Primarily such a method of measurement can help the clinician with the day to day management of the ulcer patient.

The days are long since gone when the physician had to rely on his subjective impression of the temperature of a pyrexial patient. The advent of the thermometer meant that accurate recordings could be made and these recorded graphically so that the general trend becomes immediately obvious and treatment can be adjusted accordingly. The progress of most ulcer patients, however, is still usually recorded according to subjective impressions ("healing", "progressing" etc.), and all who deal with ulcers will know how unreliable such impressions may be. In one large unit accurate measurements of ulcers were made over a period of some weeks and compared retrospectively with the recorded observatons of the several competent doctors who reviewed them at the weekly ulcer round. In not a few cases were the ulcers reported as improved when in fact no change had occurred, and in one case the ulcer had actually increased steadily in size!

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The advantages of accurate recordings may be summarised as including:

(a) to gauge accurately the progress of an ulcer towards healing;
(b) to spot at an early stage any slowing down in the rate of healing and institute requisite investigations and treatment, rather than having to wait the considerably longer time necessary for gaining the clinical impression that all is not well;
(c) to allow proper data to be gathered and enable statistical comparison to be made of factors involved in ulcer healing and treatments available;
(d) to provide permanent record of the actual condition of a patient. This is particularly important where out-patient treatment of patients lies in part with paramedical workers, in which case the method described allows the true picture to be relayed to the medical officer.

Method

Measurements of ulcers using calipers or rulers are difficult and inaccurate owing to the irregular and variable shapes of plantar ulcers. The method described allows transference onto paper of the actual outline of the ulcer, enabling both a visual record to be kept and also allowing easy determination of its area, circumference or even volume.

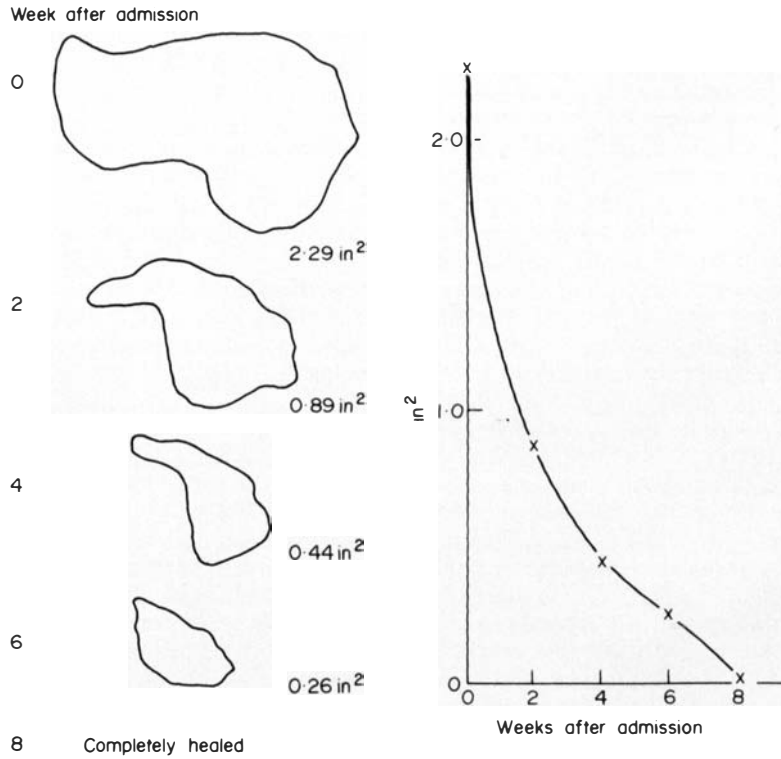

Fig. 1. Uncomplicated healing of a plantar ulcer centred over first metatarsal head of male aged 43. On admission the ulcer was infected with maggots and five days of antibiotics were given. Note the smooth curve of healing.

Two techniques have been found successful. In the first, a square of transparent celluloid, obtained by deemulsifying x-ray film is placed overlying the ulcer. The ulcer may clearly be seen through the celluloid and its outline traced with ball-point or wax pencil. The square is then removed and placed over a piece of carbon paper in the allotted section of the patient's notes. By drawing over the tracing with a stylus or ball-point the outline is transferred onto the paper as a permanent and accurate record. In the second technique, a small square of glass is used. Over this is placed firm polythene, onto which the outline is drawn. The polythene may then be removed, placed over the carbon paper and the outline transferred as before.

The latter method has the advantage that the ulcer may be seen very clearly

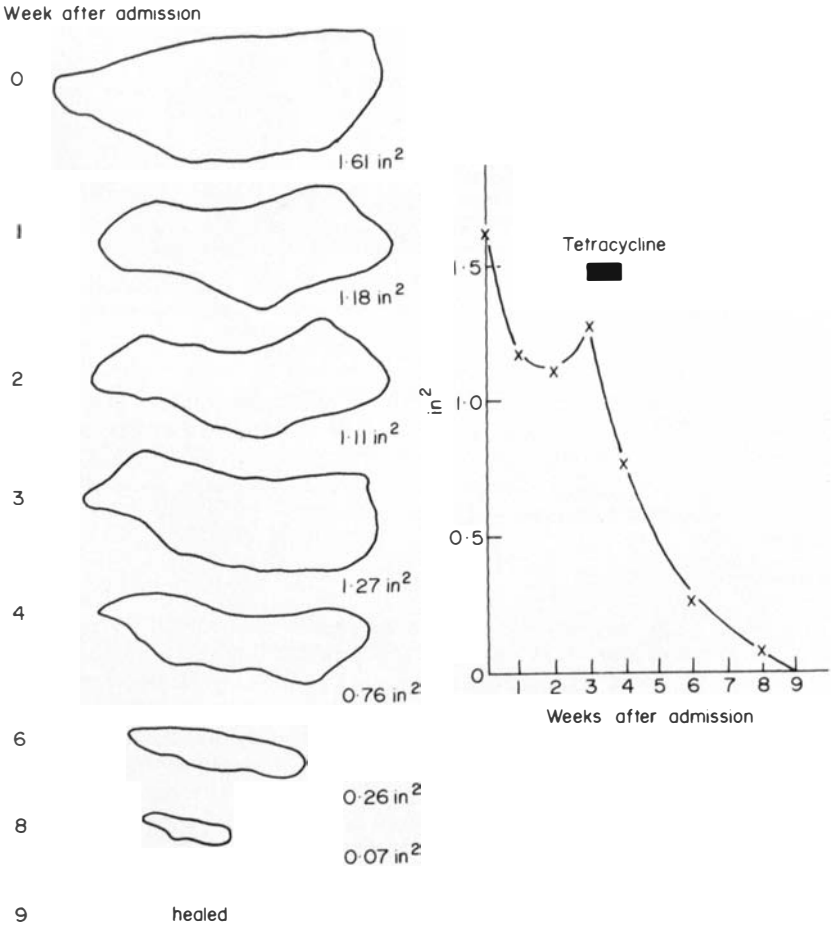

Fig. 2. An ulcer over metatarsal heads 2-4 of male patient aged 25. A slow down in the rate of healing was noted at the end of the second week and strict bed rest was enforced. At week three the charting showed the ulcer to have slightly increased in size. The ulcer appeared clean and if it were not for the charting it is unlikely that any suspicion would have been aroused. However, the graph gives an indication of possible subclinical infection and a dramatic response is shown to seven days tetracycline, after which a normal smooth healing curve is obtained.

Fig. 3. In mountainous terrain much out-patient care must lie with the paramedical work. Here a p.m.w. makes an accurate record of the ulcer of a patient living 5 days walk from the hospital.

and being firm is easier to trace. The former is useful particularly in out-patient village work in that the celluloid squares may be discarded after use and a fresh square used for each patient, thus avoiding any risk of cross-infection. The glass squares must be thoroughly cleaned after use, but the use of several squares prevents this becoming a burdensome procedure.

Discussion

The record obtained gives a week-by-week picture of an ulcer's progress. It is usually sufficient to leave it as a series of pictures allowing visual comparison, but if the area is measured it may then be charted graphically. This is quite simply determined by placing over the outline a transparent grid and counting the squares occupied by the ulcer, or alternatively by tracing the outline onto graph paper in the first place. The depth of the ulcer may be measured with a graduated probe. An ulcer healing without complication shows week by week a diminishing outline, and a smooth curve is obtained when graphed (Fig. 1). Any slowing down in rate of healing may be spotted immediately using this method, often long before clinical impressions would alert one to this fact, with consequent saving in delay of institution of investigation and treatment (Fig. 2).

This method of measurement and recording has been learned by nursing staff, physiotherapy technician and paramedical workers, all of whom find that it takes little time and effort, certainly less than writing a full description of an ulcer's shape and measurements. Notes as to the position of the ulcer and any special features should of course be appended.

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Nerve Involvement in Leprosy—Pathology, Differential Diagnosis and Principles of Management

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Nerve damage in non-lepromatous leprosy and in "reversal" reactions is the result of an immune response to the presence of antigenic material derived from leprosy bacilli within nerves. This immune response damages nerves by intra-neural epithelioid cell formation, and by compression of Schwann cells due to inflammatory oedema. In lepromatous leprosy the presence of leprosy bacilli induces slow damage to both perineurium and Schwann cells. When Erythema Nodosum Leprosum (ENL) develops, associated neuritis is probably brought about by the presence of ENL lesions within the nerves.

In the absence of typical skin lesions, the nerve damage caused by leprosy can mimic other conditions. The differential diagnosis in such cases is outlined, and the principles of management of nerve damage due to leprosy are summarised.

Some Definitions

NERVE INVOLVEMENT

This is a general term, meaning anything from the presence of a leprosy bacillus in a nerve to the total destruction of the nerve.

NERVE DAMAGE

This implies that the presence of bacilli in a nerve or the tissue response to their presence, has caused structural alterations in the nerve. The mere presence of bacilli in a nerve need not be associated with nerve damage.

Nerve damage is recognized more readily histologically than functionally. Nerves that are clearly abnormal histologically can function without recognisable impairment. For instance, about 30% of the sensory fibres in a nerve must be destroyed before alterations of sensory acuity in the area it subserves can be detected.

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However, nerve damage is usually interpreted in the clinical sense, that is, there are recognisable changes of nerve function. These can be detected by sensory testing (Pearson and Weddell, 1971), or by testing motor function by voluntary muscle power tests (VMT) (Goodwin, 1968). In some circumstances electromyographic techniques can be a sensitive guide to the progress or resolution of nerve damage (Sheskin *et al.*, 1969).

NEURITIS

Literally "inflammation of nerve", it can be interpreted in the same sense as "nerve damage". However, in this paper, "neuritis" is defined as "pain and/or tenderness of nerve". The pain may be local or referred to the area of distribution of the nerve. Nerves which show neuritis usually also show recognisable impairment of function: but function can deteriorate in the absence of pain or tenderness.

The Structure of Nerves

The axons which are the actual conducting units of nerves are enclosed by the cytoplasm of Schwann cells. The larger axons are surrounded by a myelin sheath—in this case there is only one axon per Schwann cell. Smaller axons are unmyelinated, and there may be 10 or more in a single Schwann cell.

Apart from the terminal ramifications in skin and other tissues, the Schwann cells and their axons are wrapped in bundles, or fascicles: the tissue layer enclosing each bundle is the perineurium, a compact, multilayered structure which forms a relatively impermeable barrier between nerve and interstitial fluid. The larger fascicles contain one or more capillaries which run longitudinally and form a ladder pattern of connections within the fascicle. This capillary system is fed by arterioles and drained by venules which penetrate the perineurium. Within the fascicle itself, however, it is uncommon to see any blood vessels save capillaries: and the direction of blood flow within an endoneurial capillary is unpredictable and probably variable (Lundborg, 1970).

The larger nerve trunks ("named nerves") are composed of many fascicles, which are bound together by the epineurium, a loose connective tissue sheath, which penetrates among the individual fascicles. The epineurium is vascular. Its longitudinal arterioles are fed at intervals by lateral connections from neighbouring arteries; but a normal nerve trunk can be deprived of its lateral blood supply for 15 cm or more and still maintain normal function (Bateman, 1962). Lymphatics are present in the epineurium but are not found within the individual fascicles.

Initial Considerations

1. SITES OF NERVE INVOLVEMENT

Nerves are chiefly involved in two zones, which are the same in all types of leprosy:

(a) *Skin*. The dermal nerves are microscopically involved in almost every case of leprosy, and some functional impairment can usually be detected by careful sensory testing. The subcutaneous nerves in the region of skin patches are also involved, and may be palpable.

(b) *Nerve trunks.* These large nerves are chiefly affected and damaged at specific sites ("sites of predilection"); in most of these sites the nerves
(i) lie superficially, and so are liable to be cooler than average;
(ii) lie on bony structures, and so are exposed to damage due to repeated minor trauma.

2. DIFFERENCES IN DIFFERENT TYPES OF LEPROSY

Although nerves tend to be involved at the same sites in all types of leprosy, they are damaged more rapidly at the tuberculoid end of the spectrum. The tuberculoid skin lesion, by definition shows impairment of sensation, indicating that nerve damage is an early and intrinsic manifestation of this type of leprosy. By contrast, even fairly advanced lepromatous lesions may show only partial loss of sensation, and nerve trunk damage occurs late in the disease process. Nevertheless, patients with advanced lepromatous leprosy may have very extensive and severe loss of sensation, due chiefly to damage at the dermal nerve level. Patients with borderline leprosy are at a particular disadvantage: they have extensive nerve involvement, like lepromatous cases, and are liable to get severe and rapidly developing nerve damage, like tuberculoid cases.

3. THE TIMING OF NERVE DAMAGE

Nerves tend to be damaged only in two phases of the disease:

(a) In untreated leprosy. Nerve damage is part of the natural history of the disease; and patients are often suffering from nerve damage with secondary deformity when they are first diagnosed.

(b) During the course of reactions. Both type 1 reactions (reversal reactions, upgrading reactions) and type 2 reactions (Erythema Nodosum Leprosum, ENL) can affect nerves: and so nerve function can deteriorate during the course of treatment. However, in the absence of reactions, patients receiving adequate anti-leprosy treatment usually do not develop further nerve damage, and indeed nerve function can improve (though the deformity secondary to established nerve damage may worsen).

4. IMMUNOLOGICAL CONSIDERATIONS

(a) Peripheral nerves are well protected structures. They are unaffected by pyogenic infections around them, and are never the site of tuberculomas. *Mycobacterium leprae* and some viruses are the only pathogens which regularly enter nerves.

(b) This protection is related to the structure of the nerve. In particular, the multilayered perineurium is structually well suited to a barrier function; and the endothelial cells of the intraneural capillaries have tight junctions, rendering them less permeable than blood vessels elsewhere.

(c) The relative chemical isolation of nerve fibres is also an immunological isolation. Peripheral nervous tissue can be described as an "immunological backwater".

(d) Schwann cells have a long life span; once within these cells leprosy bacilli may not be re-exposed to the extracellular environment for years. Soluble antigens may leak out, but even so the infection in this sheltered zone can escape recognition by the host defences for prolonged periods of time. This situation is in contrast to that of extraneural bacilli phagocytosed by

histiocytes; the life span of these cells is a matter of weeks only. Soluble antigens may be exposed at any time: but when the host cell dies whole bacilli are re-exposed to the extracellular environment.

The Entry of Bacilli Into Nerves

There are three possible ways in which the bacilli can enter peripheral nerves:

(1) By phagocytosis by Schwann cells in the upper layers of the dermis. These cells show "turnover" and can be actively phagocytic. Once engulfed, the bacilli could travel by contiguity from Schwann cell to Schwann cell along the nerve, or possibly within the axon. There are a number of objections to this hypothesis:

(a) There is little evidence that bacilli commonly lie freely in the dermis, (except in the rather avascular subepidermal zone in tuberculoid and borderline cases).

(b) Histologically the nerves in the middle and deeper layer of the dermis are often involved to a greater extent than the terminal nerve fibres.

(c) Bacilli are very seldom seen in axons (Boddingius, 1974).

(2) By penetration of the perineurium. However, this membrane presents a formidable barrier; in leprosy, when inflammatory cells are penetrating the perineurial layer, the nerve is usually bacillated: the invasion is the consequence of the presence of bacilli rather than the cause of their entry.

(3) Via the endoneurial blood vessels. This is the likeliest hypothesis, for there is good evidence that even tuberculoid leprosy is a systemic disease (Pearson *et al.*, 1970; Karat *et al.*, 1971); and bacteraemia is a normal finding in patients with untreated lepromatous leprosy (Drutz *et al.*, 1972). Also in early nerve involvement the bacilli tend to lie close to endoneurial blood vessels.

Much, however, is still unknown. For instance, it is not yet known whether bacilli are carried into nerves within macrophages or, lying free, adhere to the endoneurial capillaries and are thus trapped. But once they have entered a nerve, their ultimate phagocytosis by Schwann cells is probably inevitable.

The Localization of The Intraneural Infection

The sites of the body where nerves are most readily colonized and damaged are probably cooler than the average body temperature (Sabin *et al.*, 1974), and it is possible that bacilli multiply more readily in these sites. Nevertheless the focal involvement of nerve trunks appears to be more than can be accounted for in this way. Of other factors that could be involved in this localization, the most likely is trauma. When a nerve is exposed to constant minor trauma, it is likely to be mildly inflamed, and the consequent increased capillary stickiness at these sites may make bacilli or monocytes more likely to adhere and penetrate the nerve. The sites of predilection of nerves may therefore have the nature of traps for circulating bacilli. Nevertheless other mycobacteria do not enter nerves, and there is as yet no satisfactory explanation for this unique property of *Mycobacterium leprae*.

The Evolution of the Intraneural Infection

In the initial stages of the infection, Schwann cells are colonized by *Myco. leprae*, but seem to be little affected by their presence. However, after a period the Schwann cell may be destroyed, possibly by the bulk of bacilli it contains, or

by interference with its metabolic processes. The bacilli are released, and may be taken up by neighbouring Schwann cells or possibly by intraneural histocytes which could transport them via the endoneurial blood vessels along the nerve. Thus the intraneural infection can progress slowly along the nerve. In established tuberculoid leprosy, where bacilli are markedly more concentrated in nerves than elsewhere, such intraneural spread is probably the major route of dissemination of the infection.

The Host Response to the Infection

(1) TUBERCULOID LEPROSY

Nerves are "immunological backwaters"; but, as bacilli multiply within a nerve, soluble antigen leaks out of the Schwann cells into the endoneurial blood vessels and through the perineurium. Thus the infection is recognized, and the host defences mount an attack. The nerve is invaded by inflammatory cells, chiefly through the perineurial layers, possibly because the circulation in the endoneurial capillaries disperses the antigen before a critical "recognition level" is attained. The result is the formation of an epithelioid cell granuloma within the nerve; the Schwann cells and the axons they contain are destroyed in the process (see Fig. 1).

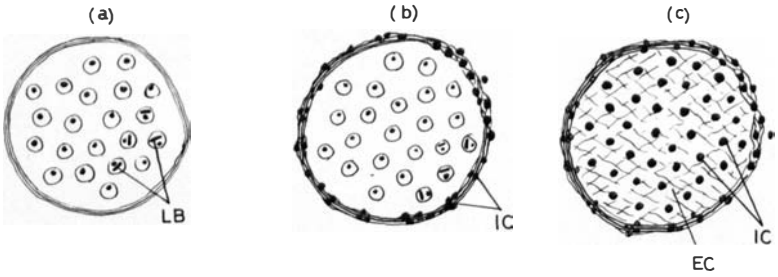

Fig. 1. The process of nerve damage in tuberculoid leprosy. (a) A nerve fascicle with a few leprosy bacilli (LB) lying within Schwann cells. (b) Inflammatory cells (IC) cluster round the perineurium and begin to infiltrate its layers. (c) Inflammatory cells (IC) have entered the nerve, with consequent epithelioid cell (EC) formation.

In tuberculoid leprosy, bacilli spread slowly along the dermal nerves: the bacillary concentration must reach a "critical level" before the infection is recognized, and attacked. If all the bacilli were destroyed, this would be a true, self-limiting infection. But normally some bacilli survive, and so the tuberculoid skin lesion slowly extends. The process may be visualized as a wave of bacillation spreading slowly through the dermal nerves, pursued but never quite overtaken by the inflammatory response. The infection is largely confined to nerves; once they are all destroyed, the bacilli are destroyed with them, and resolution by fibrosis occurs, forming the "clear centre" of the tuberculoid lesion.

(2) BORDERLINE LEPROSY

In this type of disease the nerves are attacked in the same way. But the host cells are less highly sensitized to the infection, and higher bacillary concentrations are required to elicit an inflammatory response. Bacilli are therefore present in

considerable numbers in Schwann cells, and sometimes can be seen in the perineurium. Also the process is more focal and less acute and destructive. The morphology of the nerves is better preserved, and characteristically there are zones of epithelioid cells adjacent to areas where the Schwann cells, though bacillated, are well preserved. Not infrequently the epithelioid cell foci lie next to the perineurium (and may indeed form within the layers of the perineurium (Pearson and Weddell, 1975)). In such cases the appearance is of strands of surviving Schwann cells lying in an annular zone of inflammatory tissue (see Fig. 2).

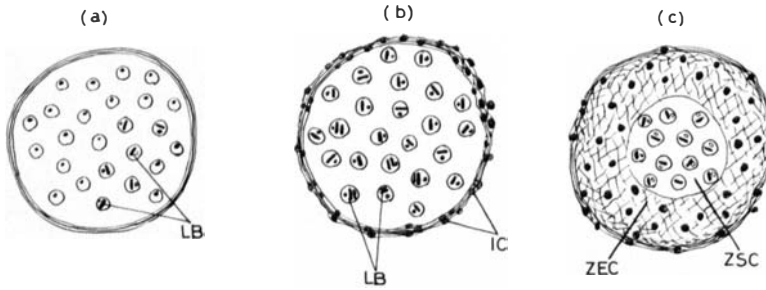

Fig. 2. The process of nerve damage in borderline leprosy. (a) A nerve fascicle with a few leprosy bacilli (LB) lying within Schwann cells. (b) The leprosy bacilli (LB) are considerably increased in number, and inflammatory cells (IC) are beginning to infiltrate the perineurium. (c) Inflammatory cells have entered the nerve, giving rise to a zone of epithelioid cells (ZEC). There is a zone of surviving bacillated Schwann cells (ZSC).

(3) LEPROMATOUS LEPROSY

In this type of disease the host preserves little or no capacity to destroy the invading mycobacteria—consequently they multiply unchecked, and in almost any situation. Thus, in nerves the bacillary concentration in perineurial cells is at least as great as in the Schwann cells, and often greater. Both sites are damaged, and the perineurial changes may be the more important in the causation of nerve damage in lepromatous leprosy.

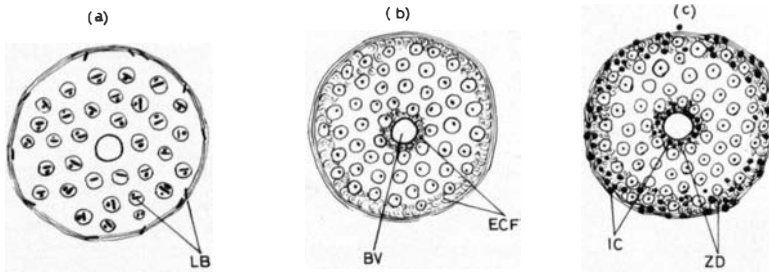

Fig. 3. The process of nerve damage in lepromatous leprosy. (a) Leprosy bacilli (LB) are seen in the Schwann cells and also in perineurial cells of a nerve fascicle. (b) Extracellular fluid components (ECF) leak through the perineurium and intraneural blood vessels (BV) into the nerve. (c) Inflammatory cells (IC) enter the nerve giving rise to zones of damage (ZD) round the blood vessel and near the perineurium.
NOTE. Leprosy bacilli have been omitted from diagrams (b) and (c).

The perineurium acts as a barrier between Schwann cells and the extracellular fluid; it plays a major part in stabilizing the intraneural environment. In lepromatous leprosy, bacillary multiplication within the perineurial cells appears to initiate the breakdown of this barrier; the process can be visualized as the formation of a series of "micropunctures" in the perineurium. There are two consequences of this "perineurial incompetence" (Fig. 3):

(a) Extracellular fluid components can enter the nerve; this can impair the function of Schwann cells. Such impairment appears, on occasions at least, to be reversible, and may account for the very rapid improvement of nerve function that sometimes occurs in the early months of treatment of lepromatous leprosy.

(b) The nerve appears also to be more vulnerable to the entry through the perineurial layers of inflammatory cells. Thus, in the nerve zone immediately adjacent to the perineurium there can be seen a "zone of damage" where inflammatory cells are present in higher concentration than in the rest of the nerve, and where the Schwann cells have sustained more damage. Similar zones of damage are to be seen around the intraneural blood vessels, whose endothelial cells often contain large numbers of bacilli, and which have been shown in experimental leprosy to be abnormally permeable (Boddingius *et al.*, 1972).

Experimental damage to the perineurium has been shown in normal animal nerve to elicit a cellular response which has the effect of repairing the damage (Morris *et al.*, 1972). In patients with lepromatous leprosy this process can be most clearly seen in the dermal nerves; the end result is the transformation of the perineurium into a wide "perineurial zone" made up of multiple strands of perineurium, which take on a thick fleshy appearance, and whose cytoplasm contains many bacilli. The layers of perineurium are infiltrated with inflammatory cells, chiefly histiocytes and plasma cells; and on occasion the layers are solidly filled with cells, giving an onion peel appearance. There are usually a higher concentration of bacilli in the perineurial zone than in the surviving Schwann cells.

The mechanism which causes this appearance is by no means certain. In the experimental situation of Morris *et al.*, 1972 it was clear that Schwann cells took part in the process of perineurial repair; they formed circumferential elongations around groups of other Schwann cells, thus giving rise to a "pseudoperineurium", which in time became organized till it was indistinguishable from normal perineurium. Thus, under their experimental conditions Schwann cells could metamorphose to take on the form and function of perineurial cells.

It is likely that a similar process occurs in leprosy, in an attempt to repair the perineurial damage. The process is shown diagrammatically in Fig. 4. Schwann cells in the region of perineurial micropunctures divest themselves of their axons, extend lateral processes and apply themselves as "patches" to the damaged area. However, the Schwann cells themselves will probably be or become bacillated, and the patching process, though unlikely to be functionally effective, will be liable to continue, thus giving rise to the multilayered perineurial appearance. As this process continues, the number of Schwann cells will slowly decrease, and so the nerve will slowly be damaged, and finally destroyed.

If this hypothesis is correct, it accounts for the fact that in lepromatous leprosy there is often remarkable preservation of motor nerve function even in advanced cases with severe dermal nerve damage and sensory deficit. If the process of

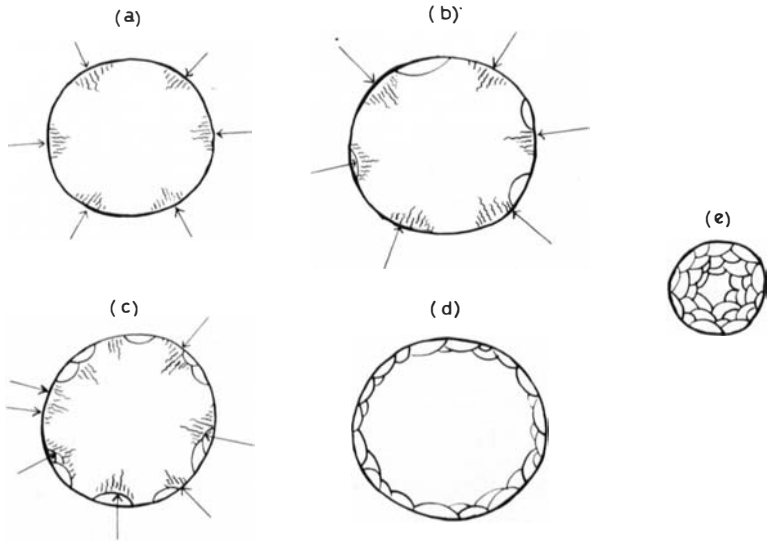

Fig. 4. The possible sequence of events which causes the multilayered appearance of the perineurium in lepromatous leprosy. →, site of "micropuncture"; *SSS*, zone into which extracellular fluid components leak. (a), (b), (c), and (d) show the evolution of this appearance, (e) shows a small nerve almost destroyed by a depth of multilayering which leaves a larger nerve (d) largely intact.

damage involves the slow destruction of Schwann cells and their incorporation into the perineurial layers, it is likely to extend gradually into nerves, and should spread at much the same rate regardless of the diameter of the nerve. Thus a small nerve can be fully destroyed at a time when a large nerve is only affected at its periphery, and still retains the majority of its functional capacity (Fig. 4(e)). In other words, leprosy does not have a predilection for sensory nerves, but in lepromatous leprosy it takes much longer to destroy the larger nerves.

Final proof of the part played by Schwann cell metamorphosis in the development of the nerve damage in lepromatous leprosy will require much experimental work; but it is clear that perineurial damage, however caused, and whatever its consequences, plays a major part in the causation of nerve damage in lepromatous leprosy.

(4) TYPE 1 REACTIONS (REVERSAL OR UPGRADING REACTIONS)

These reactions occur most characteristically in borderline leprosy, and tend to develop in the early months of treatment, though much the same process can occur in untreated cases. They are associated with an increase of the immune response of the host cells to certain antigens of *Myco. leprae*, and are clinically characterized by the development of increased oedema and erythema of skin lesions. Nerves are commonly involved, and can be rapidly damaged, sometimes with little or no pain or tenderness.

Histologically the nerves in borderline leprosy can be considered as consisting of strands of surviving Schwann cells in tubes of rather rigid inflammatory tissue (Fig. 5). They are clearly very vulnerable to pressure; and in the early stages of

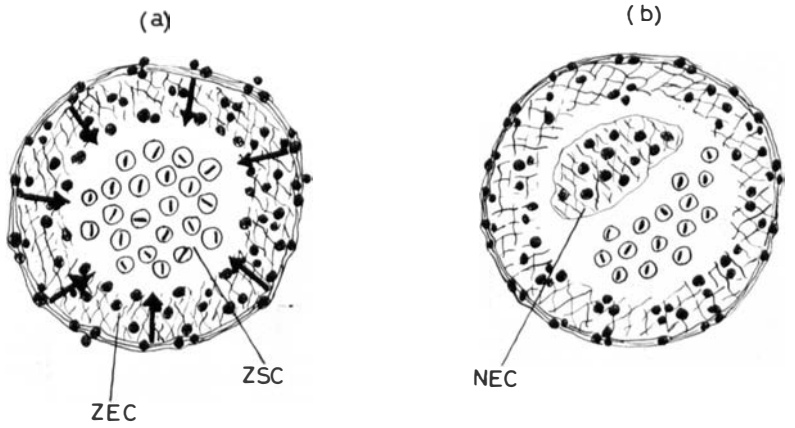

Fig. 5. The process of nerve damage in "reversal" reaction. (a) Oedema of the epithelioid cell zone (ZEC) causes compression of the surviving zone of Schwann cells (ZSC). (b) Shows formation of new epithelioid cells (NEC) in the zone of surviving Schwann cells.

Type 1 reaction the first and invariable histological feature is increased oedema of the granuloma. Thus the surviving strands of Schwann cells are liable to be suddenly compressed, and nerves can lose their function extremely rapidly for this reason. If the pressure is relieved before demyelination occurs, function can recover within a few days; if the axons have been demyelinated, recovery will require longer, probably several weeks. If the pressure is sufficient and prolonged enough to cause actual interruption of the axons, recovery must be delayed till regeneration occurs, usually several months.

Compression, however, is not the only way in which these nerves can sustain damage. The increased sensitivity of the host cells may be sufficient to cause further epithelioid cell formation within the nerve if the concentration of bacillary antigen in the surviving Schwann cells is sufficient to trigger the response. In these circumstances the same response will occur as is seen in the untreated disease; inflammation within the nerve, with consequent destruction of the Schwann cells and their axons. Permanent and irreversible nerve damage is liable to ensue.

(5) ERYTHEMA NODOSUM LEPROSUM (ENL)

This reaction appears to be the consequence of the formation of antibody/antigen complexes (immune complexes), which are toxic and cause tissue damage. They can form wherever there is bacillary antigen present, and though the name implies that it is a skin condition, lesions can cause neuritis, orchitis, lymphadenitis, and even polyarthritis, and renal involvement (presumably associated with the deposition of circulating immune complexes).

At the clinical level, the chief difference between the neuritis associated with ENL and that occurring in Type 1 reactions is that nerve damage occurs much more slowly in the former. In reversal reactions, there can be rapid nerve destruction with little neuritis. In ENL nerves can be painful and tender for prolonged periods, and still show only mild loss of function. Thus the treatment

of neuritis in ENL is much less urgently required than that of nerve involvement in Type 1 reactions, even though the symptoms may be more severe.

The pathological changes associated with neuritis in patients with lepromatous leprosy are less fully understood than are those of Type 1 reactions. ENL tends to occur in patients who have been treated for some months or years; in these cases the processes of resolution of the dermal nerve involvement due to uncomplicated lepromatous leprosy have been largely completed. Indeed biopsies in such cases not uncommonly show well preserved and apparently protected and spared small dermal nerves lying close to or within foci of polymorphs in skin ENL lesions. The fact that ENL nodules tend to be very tender also implies that the nerves are functioning efficiently; the pain is probably chemically induced by the release of active substances such as polypeptides from damaged cells in the vicinity of the nerves.

In nerve trunks, biopsies taken when the nerve is painful and tender will, on occasion, show the presence of ENL lesions of the same sort as are seen in skin. But this is by no means invariable; not uncommonly such biopsies show surprisingly little abnormality, merely scattered inflammatory cells among the Schwann cells. The reason for this is uncertain: possibly the biopsy was taken too late, after the lesion had resolved, or possibly there was a localized ENL lesion elsewhere in the nerve. Or it is possible that when ENL affects nerves its manifestation can differ from that seen in skin.

If the neuritis seen in patients with lepromatous leprosy, and often accompanied by ENL of the skin, is indeed a different process from that seen in

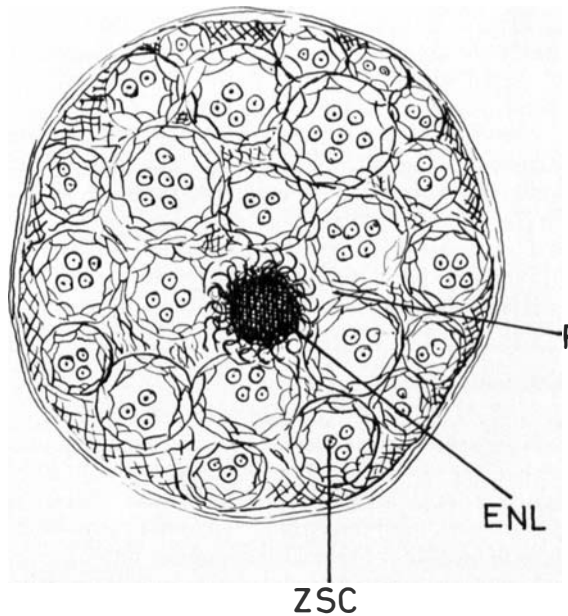

Fig. 6. The process of nerve damage in ENL. There is an ENL focus (ENL) within a nerve trunk. It lies between zones of surviving Schwann cells (ZSC) among the layers of perineurium (P).

the skin, this could account for the slowness with which nerve damage occurs in these cases. But even if actual ENL nodules form within nerve trunks, as is sometimes demonstrated, there is a possible explanation for the unexpectedly slight damage they usually cause. The nerves in such patients are usually severely damaged, the process of perineurial "proliferation" is far advanced, and the whole structure of the nerves distorted by the ingress of inflammatory cells. Indeed it is often difficult to recognize that such biopsies are composed of neural tissue. Moreover, as in untreated lepromatous leprosy, there is a tendency for the bacillary concentration to be greater in the perineurial zone. Thus it is possible that ENL lesions, which tend to develop in areas of higher bacillary concentration, will occur chiefly in perineurial areas, and thus be less liable to damage the surviving Schwann cells (Fig. 6).

Differential Diagnosis of Nerve Involvement

(1) LEPROSY AND OTHER DISEASES

The salient facts to bear in mind so far as the neurological changes in leprosy are concerned are:–

(a) Localized irregular nerve enlargement is almost always due to leprosy.
(b) Muscle weakness is always due to lower motor neurone damage, and almost never attacks proximal limb muscles, limb girdle muscles, or the trunk musculature.
(c) In early cases of leprosy sensory loss shows a mixture of "named nerve" distribution together with localized areas of impaired sensation due to dermal nerve damage in skin lesions.
(d) A "glove and stocking" pattern of sensory loss can be found, usually in more advanced cases. But careful sensory testing will almost always reveal small islands of preserved sensation on the feet and hands. Also the tendon reflexes are preserved in these cases, and are often brisker than usual.
(e) Position sense is almost always preserved.
(f) The central nervous system is never damaged by leprosy.

Diseases most commonly confused with leprosy include:–

(a) Those associated with spinal cord abnormalities, such as syringomyelia, amyotrophic lateral sclerosis, and motor neurone disease.
(b) Those associated with peripheral nerve lesions.
    (i) Damage by pressure, such as spinal root compression, the carpal tunnel syndrome and Bell's palsy.
    (ii) Polyneuritis, which may be:–
        Hereditary – Hypertrophic interstitial neuropathy, peroneal muscular atrophy.
        Metabolic – Diabetes mellitus, porphyria, amyloidosis.
        Deficiency – Vitamin B1 or B12 especially, precipitated by malabsorption, alcoholism, or other malnutrition.
        Toxic – Lead, mercury, arsenic.
        Industrial and therapeutic chemicals.
        Diphtheria and other infections.
        Malignant – Particularly with carcinoma of the bronchus.

(c) Those associated with muscle disease, including the hereditary myopathies and myositis.
(d) Those associated with "trophic" changes, including diabetes mellitus, tabes dorsalis and congenital indifference to pain.

In most cases awareness of these possibilities, together with a full history and clinical examination, are sufficient to make the correct diagnosis.

(2) DIFFERENT TYPES OF NERVE DAMAGE IN LEPROSY

There is seldom a problem of differential diagnosis in patients newly presenting with untreated leprosy and nerve involvement. Once the type of leprosy is know the process occurring in the nerves can be considered reasonably certain. It is unusual in these cases for very rapidly progressive nerve damage to be occurring, and in general the initiation of anti-leprosy treatment will control the progress of nerve damage. The more common problem is that of patients who develop nerve involvement during the course of treatment. In such cases also, however, the key to diagnosis is the classification of the disease.

In tuberculoid leprosy, borderline leprosy and Type 1 reactions the mechanism of nerve damage is almost identical, differences being related to the phase of the disease and to the severity and suddenness of onset. Even untreated cases can develop a fairly sudden increase of oedema and erythema of their skin lesions together with neuritis; and clinically the distinction between active leprosy, very active leprosy, and reaction probably cannot be defined. In the times before effective treatment was known, such reactions tended to leave the patient closer to the lepromatous end of the spectrum, and have therefore been called "downgrading" reactions (Ridley, 1969). However, it seems likely that they are brought about by the same mechanism as in "reversal" reactions, namely, an increased immune response to bacillary antigens; and these downgrading reactions are probably best considered to be host responses to antigens which are not concerned with resistance to the infection.

Thus, nerve involvement, whether detected by the patients' subjective symptoms, by the presence of neuritis, or by tests to assess nerve function, represents the same process in non-lepromatous leprosy, namely the damage of nerve tissue by the host response to mycobacterial antigens contained in the nerve. It is an unwanted part of the immune response to the infection. Any patient with non-lepromatous leprosy is liable to develop such nerve involvement, either before treatment starts or during treatment so long as there is bacillary antigen remaining in the nerves.

In lepromatous leprosy under treatment, nerve damage, with or without neuritis, is commonly associated with ENL lesions in the skin; and whether such lesions are present or not, the nerve involvement probably represents the same process, namely immune complex formation occurring within the nerves. Occasionally, however, patients with subpolar lepromatous leprosy can develop severe nerve damage associated with epithelioid cell formation within the nerve, although there may be no sign of Type 1 reaction in the skin.

Principles of Management of Nerve Involvement

Nerve damage occurring in the course of the untreated disease may be irreversible, but it is usually arrested by the initiation of anti-leprosy treatment. If however, the disease is unusually active and nerves are being acutely damaged,

management should be on the principles outlined below for the treatment of nerve involvement in reactions.

When nerves are being damaged in the course of treatment, it is normally because a reaction is present. Such reactions can occur in nerves without affecting the skin; this is presumably related to the different concentrations of bacillary antigen in different sites, and particularly to the way in which bacilli can survive for prolonged periods in nerves, even in non-lepromatous cases.

(1) NERVE DAMAGE IN "REVERSAL" (TYPE 1) REACTIONS

In non-lepromatous leprosy nerve damage is caused by the immune response of the host. The appropriate therapy therefore is immunosuppression, and the usual drugs those of the corticosteroid group. The possibility of very rapid and severe nerve damage in such cases should encourage the use of steroids. They relieve inflammatory oedema, and so lessen nerve compression; and by their immunosuppression prevent further epithelioid cell formation within nerves.

Steroid therapy must be in adequate dosage to control the reaction, and continued until the conditions which precipitated the reaction are no longer present; this means, until the concentration of bacillary antigen in the nerves is reduced to a level that no longer elicits an immune response. In most cases, the period required is a few months, so the dangers of ultra long term treatment with steroids are unlikely to occur. Dosage levels higher than prednisolone 30-40 mg daily are seldom required, and can usually be reduced to about 20 mg daily after 4-6 weeks. It is important to continue anti-leprosy treatment, and there is little evidence that the drug or dosage employed influences the end result.

(2) NERVE DAMAGE IN ENL (TYPE 2) REACTIONS

In lepromatous leprosy neuritis is not uncommon, and may or may not be associated with the presence of ENL lesions in the skin. However, loss of function is much slower to develop than in reversal reactions. Nerves can be tender and painful and yet function well; and patients can show nerve tenderness for months and still develop little or no deterioration of function. This consideration is the major reason for the different management of neuritis in lepromatous leprosy, in which the corticosteroids should not be used in the first instance, but reserved for patients showing nerve damage as well as neuritis. When nerve function is not deteriorating the "standard" drugs for the treatment of ENL should be employed; these include chloroquin, stibophen (fouadin), analgesics, and, in more severe cases, clofazimine and thalidomide. Local treatment, particularly splinting, is often helpful in relieving pain, as are perineurial injections of local anaesthetic and steroids. The place of surgical treatment in the management of nerve damage has yet to be determined.

When treating patients with ENL and neuritis, the normal pattern of the condition should be borne in mind. ENL is usually episodic; an attack can last for a week or two, but may not recur for weeks or months. Corticosteroids, if indicated, should be prescribed on this principle; fairly high dosages (say 30 mg prednisolone daily) are likely to be required only for a few days, and the dosage should be rapidly reduced, the whole course lasting no longer than 2-3 weeks, and repeated as necessary if severe neuritis recurs. The occasional patient who develops prolonged uninterrupted neuritis associated with nerve damage or severe ENL may require continuous steroid treatment; but the requirement can usually be much reduced by the concomitant use of clofazimine and/or thalidomide.

Anti-leprosy treatment must be continued, and there is little evidence that the drug or dosage employed affects the result. (Clofazimine is of value because of its anti-inflammatory activity: its anti-leprosy action is an incidental benefit.)

(3) ESTABLISHED NERVE DAMAGE

Although much nerve damage in leprosy is in practice unpreventable, it need not lead on inevitably to the deformities which are the popular hallmark of the "leper". Deformity of the hands and feet in leprosy is associated with tissue injuries (in anaesthetic limbs) and muscle imbalance due to motor nerve damage and consequent weakness of certain muscle groups. But the stiffness of joints is due to failure to put them through full range movements regularly. Simple health education, aiming to teach patients the hazards of anaesthesia and how to avoid them; skin care, and particularly, the early treatment of minor injuries; and simple exercises to be performed for a few minutes daily, can largely prevent the development of deformities even if there is permanent nerve damage.

Acknowledgements

We are most grateful to Miss Jane Neville, who drew the diagrams, and to Prof. A. G. M. Weddell, who shared in most of the histopathological studies summarised here. He and many other colleagues have stimulated us in discussions and advised in the preparation of this paper.

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News and Notes

REHABILITATION AND PUBLIC RELATIONS

The 4th International Symposium on the Rôle of Public Relations in Rehabilitation was held in Athens from 10 to 16 May, 1975 under the joint auspices of the Ministry of Culture and Sciences and the Ministry of Social Services.

A message of greeting from the International Leprosy Association was read at the inaugural session.

Although most of the participants were from the affluent countries of Europe and North America, and although the Symposium was mainly concerned with the diseases and conditions common in the Western world, two leprosy workers directed their attention to the needs of a special class of underprivileged persons needing rehabilitation. Dr S. G. Browne (a member of the Executive Committee of the International Society) gave a stimulating paper on "Relations with Inpatients and Outpatients with Special Reference to Leprosy Sufferers", and Dr A. J. Salvapandian, Professor of Orthopaedic Surgery at the Christian Medical College, Vellore, spoke on "Public Relations in Leprosy Rehabilitation".

The facts about leprosy and the need for local knowledge of the sufferer and the community were stressed by both speakers, and these ideas – novel in such a gathering – were welcomed and appreciated.

LEPROSY IN GREECE

During the above Symposium, Dr Browne was able to make fruitful contact with the Minister of Social Services and Health, and his officials, discussing with them the outmoded law requiring compulsory and virtually lifelong isolation of all persons in Greece diagnosed as having leprosy. At present, 380 leprosy sufferers are confined to the Santa Barbara Leprosy Hospital, but moves are afoot to amend or abrogate the law. The main obstacle to progress along these lines is the prejudice of ordinary people, and the misconceptions about leprosy that are widely current. In two television programmes, Dr Browne attempted to dispel some of these misconceptions by substituting modern ideas about leprosy and its control. He said that isolation as practised was inhuman, expensive, unnecessary and ineffective.

AFRICAN JOURNEYS

Dr S. G. Browne has recently made two journeys to Africa in the interests of leprosy sufferers. The first took him to Libya, where he advised the Government on the leprosy problem in the country, and to Cairo, where he took part, with Professor R. Van Breuseghem (of Antwerp) in a Symposium on Leprosy and Mycotic Diseases.

The second journey, sponsored by The Leprosy Mission as an initiatory phase of part of its Centenary outreach, was to Zaïre, and was particularly directed to conducting seminars for leprosy workers. With Dr J. Cap (now of ALERT, Addis Ababa) and Professor H. Périer (Adviser to the Zaïre Ministry of Health on Transmissible Diseases), Dr Browne was asked to draw up an advisory document on leprosy control in Zaïre. There may now be close on half a million cases of leprosy in Zaïre, in a population approaching 25 million people. Two Belgian voluntary bodies – *Foperda* and *Les Amis du Père Damien* – sponsored the attendance of several participants at these two seminars.

XV INTERNATIONAL CONGRESS OF DERMATOLOGY

The XV International Congress of Dermatology will take place in Mexico City from 10 to 22 October, 1977, under the auspices of the International Committee of Dermatology of the International League of Dermatological Societies. The Honorary President of the Congress will be Professor Fernando Latapi.

A very full programme of Symposia, Lectures, Patient Presentations, Workshops, etc., is being arranged. Leprosy will be among the main subjects selected for the symposia.

The Secretary-General of the Congress will be:

Professor Felix Sagher,
Department of Dermatology,
Hadassah University Hospital,
P.O. Box 499,
91 000 Jerusalem, Israel,

to whom all enquiries should be sent.

In the large auditorium, simultaneous translation will be available in English, French, German and Spanish. Abstracts (200 words, in English only) are to be submitted by I January, 1977.

SEMINAR IN GUYANA: APRIL 4-6, 1975 "LEPROSY IN COMPREHENSIVE COMMUNITY HEALTH CARE"

The Medical Research Council of Guyana recently organized an intensive three-day seminar on leprosy, which was held in the University in Georgetown and attended by over 200 medical and paramedical workers. The guest lecturers were Dr O. W. Hasselblad of American Leprosy Missions, U.S.A., Dr M. L. Brubaker of the Pan-American Health Organisation (W.H.O.) and Dr A. C. McDougall, British Leprosy Relief Association, U.K. In company with the Government Leprologist, Dr Patricia Rose, the lecturers had numerous preliminary meetings with Ministry of Health and University officials, and before the opening of the Seminar the new LEPRA film was shown on three separate occasions and enthusiastically received by lay and medical audiences. The Seminar opened with a lecture and discussion on "Basic Definitions and Concepts of Leprosy," followed by "Leprosy in the Americas," "Early Signs and Symptoms," "Immunology and Complications," "Comparative Histopathology of Granulomatous Lesions" (Dr E. Simon, Pathologist, Georgetown Hospital), "Epidemiology and Control" (Dr Patricia Rose), "Causes of Physical Disabilities," "Problems and Prospects in Leprosy Research," "Psychosocial Aspects of Leprosy," "The Leprosarium in the Changing Pattern of the Management and

Control of Leprosy" and "Symptom Patterns of Clinical Leprosy in Guyana" (Dr Patricia Rose).

During the past three years admissions to Mahaica Leprosarium have fallen virtually to zero, and this institution is now largely concerned with the care of patients who are aged, blind, institutionalised or in advanced stages of physical deformity. Nearly 800 out-patients have been registered by Dr Patricia Rose and her team, and initial diagnosis, treatment and supervision are now established in the more densely populated areas on an entirely out-patient basis.

The figures for leprosy in Guyana and the available resources are such that the disease could be reduced to very low levels within the foreseeable future. The enthusiasm shown by both lay and medical audiences for the LEPRA film was matched during the Seminar itself, where the lecturers gave emphasis to the wider involvement of the community in leprosy control and to its acceptance into comprehensive community care.

"LE SECOURS AUX LÉPREUX (CANADA) INC"

In 1961 a young Canadian nurse working in association with leprosy patients at Pollambakam (India), wrote to her uncle in Montreal, describing her work, its needs and its problems. His sympathy and enthusiasm were aroused, and in 1964 he began to circulate a bulletin of leprosy information among friends and interested people in Canada. From these small beginnings there has developed over the past 10 years a major charitable organisation dedicated to the relief of sufferers from leprosy, the annual receipts of which jumped from $5950 in 1964 to $765,000 in 1974. The Society is an active and influential member of the International Federation of Anti-Leprosy Associations (ILEP), and its founder, Mr Théorêt has been elected President of ILEP for 1975.

"Le Secours aux Lépreux (Canada)" is a non-governmental and non-confessional Association; it cooperates with all other ILEP member Associations, and is prepared to contribute to any acceptable project irrespective of language, race or creed. We offer congratulations and best wishes to Mr Théorêt and the Directors of the Association.

GANDHI MEMORIAL LEPROSY FOUNDATION

The Annual Report of the Gandhi Memorial Leprosy Foundation for 1973-74 makes interesting reading. The work of the Foundation, summarized in the September 1974 Issue of *Leprosy Review* (Vol. 45, 274), has been fully maintained in all its varied aspects. Of particular interest is the initiative taken by the Foundation to emphasize to the Government of India the need for a higher allocation of funds for leprosy control during the forthcoming Fifth Five-year Plan period. Following a meeting of leading leprologists and other experts called together by the Foundation, an approach paper for national leprosy control work in the Fifth Five-year Plan was presented to Government, and a delegation of four members of the Foundation met the Honourable Prime Minister herself. As a result of her interest an allocation of Rs. 33 crores has been provisionally sanctioned for the National Leprosy Control Programme during the Fifth Five-year Plan.

TUBERCULOSIS, STILL A MAJOR HEALTH PROBLEM

The ninth report of the WHO Expert Committee on Tuberculosis contains interesting reading for leprosy workers. Estimates for the number of infectious tuberculosis cases in the world today, at the range of 15-20 million are very similar to those for sufferers from leprosy. In discussing the organisation of national tuberculosis programmes the report underlines the essential features of any comprehensive anti-tuberculosis programme as follows; it must be country-wide, and permanent rather than a crash programme or one time endeavour; it should match the attitudes and customs of the community and be adapted to the convenience of the consumers rather than of those providing the service; it must be developed as a well balanced component of the national health programme and fall within the range of available resources; the case-finding and treatment programme should be developed as an entity, and treatment should be free of charge and primarily ambulatory. Here are perfect terms of reference for all responsible for organizing leprosy control.

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In Memoriam

Dr Kok of the Westfort Institution, Pretoria, Union of South Africa has informed us of the death of Dr A. R. Davison, well known among the older generation of leprologists for his independent and outspoken approach to leprosy and its problems. Dr Davison gave many years of his life as Superintendent at Westfort to the care of sufferers from leprosy, and we add our tribute to the memory of a distinguished and devoted colleague. The following appreciation is reprinted with permission from the South African Medical Journal of 21 December, 1974.

ARTHUR RUSCOE DAVISON

M.R.C.S. (ENG.), L.R.C.P. (LOND.)

Dr J. H. Struthers, of Pretoria, writes:

Dr Davison was born in March 1901 in Queenstown. He attended Rondebosch Boys' High School and the University of Cape Town, then furthered his studies in London.

In 1926 he accepted a temporary appointment as Medical Officer at the Robben Island Leprosy Institution. Thereafter he became Medical Officer at the Leprosy Institution at Emjanyana in the Transkei, where he worked for 13 years. In 1939 he was promoted to the post of Medical Superintendent of the Westfort Institution in Pretoria, where he worked for a further 25 years, until he retired to Durban in March 1964.

Dr Davison devoted his life to work in this field, and became a well-known leprologist. He attended international congresses on leprosy in Madrid, Cuba and Japan, and visited leprosy institutions in South America as well. He was privileged to see the results of diaminodiphenyl sulphone treatment, which was first used in 1943*, and which changed the institutions from places of desolation to places of hope. Whereas before there had been only isolation and expectation of eventual death in these institutions, patients could look forward to the promise of a cure, and the hope of a return to their homes.

Dr Davison died on 18 October 1974, at the age of 73 years. He will especially be remembered for his great kindness, and for the wonderful sense of humour that meant so much to his patients during his 39 years of devoted service to them.

Our deepest sympathy goes to his wife Doris, to his daughter Mrs D. Tovey and family, and to his son Dr John Davison and family.

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* The correct year was 1947 – Ed.

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Leprosy and the Community

LEPROSY IN THE SUDAN GEOGRAPHICAL DISTRIBUTION AND PREVALENCE

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Introduction

Very little is known about the distribution and prevalence of leprosy in the Sudan. Accurate statistical data are not available because systematic attempts at case detection have been few and limited in scope. Most available information is derived from statistics from hospitals or leprosy colonies, giving the number of patients in them. Over 80% of patients inhabiting these colonies are severely disabled and burnt-out cases. As leprosy is still a highly stigmatizing disease among most of the tribes, it becomes obvious how misleading such statistics can be.

The geographical distribution of these colonies, and the number of patients in them, are nevertheless a relatively accurate index of the endemicity of the disease in those areas. I can say this with a reasonable degree of confidence as I have visited most of these areas and recorded the actual homes of the patients. Some exceptions, e.g. Khartoum, will be mentioned later.

Leprosy in the Northern Region

This vast expanse of land lies between latitude 12°N and 22°N. Its topography is either desert or semi-desert with few shrubs. With the exception of those living in towns, the inhabitants of this region are either farmers clustered along the Nile valley or nomads moving in the open with their sheep and camels.

The Region includes the whole of the Northern Province, the Red Sea Province, Northern part of Kassala, Kordofan, Darfur and most of Khartoum Provinces. It has been the general impression of all medical workers as far back as 1908 (Balfour, 1908) that leprosy is scarce in the region. This impression holds good up to the present day.

The Northern Province

Small foci of high endemicity are known to exist in this Province. A few cases were reported around Al-Daba and Merowi, and two other foci are located near Atbara and Shendi respectively. People in this Province are relatively sophisticated, and leprosy patients are either strictly confined or prefer to migrate further south to larger towns. Some go further south to join colonies in the highly

endemic areas. Only 25 patients, all hospital cases, are now recorded in this Province with a population of 1.2 millions.

Khartoum Province

The three main towns in this Province comprise the capital of the Sudan, its population totalling 1.4 millions. All leprosy cases live in these towns. Five hundred and seventy cases were recorded in 1972, almost all coming from the highly endemic areas in Southern Province of Kordofan, South Darfur and the three Southern Provinces. Very few indigenous cases are reported. Apart from patients seen in the dermatology clinics, two other main clinics for leprosy are worth mentioning.

(a) The Church Mission Clinic. This is a mobile clinic supervised by an experienced expatriate sister assisted by a nurse with some leprosy training. They visited some 358 patients who live in different sectors of the town.
(b) The Swiss Mission Clinic. Leprosy cases are seen as part of a general outpatient clinic run by an expatriate doctor.

Patients are seen weekly and receive their treatment regularly. A 24 bed leprosy ward is under construction in Khartoum hospital.

The Red Sea, Northern Kassala, Kordofan and Darfur Provinces

These can be regarded as leprosy-free areas.

Leprosy in the Central Region

This fertile clay land extends from the verges of the semi desert at 12°N latitude to the rich savannah at latitude 10°N. Except for the highlands along the Ethiopian border and some scattered hills, the land is flat and fertile, with agriculture and animal husbandry the main means of livelihood of the inhabitants. This region includes the Blue Nile Province, Southern Kassala, Southern Kordofan, Southern Darfur and a small part of Khartoum Province.

There are three areas of high leprosy endemicity in this region.

(a) *Southern Kordofan (The Nuba Mountains)*

The Nuba tribes inhabit these hilly areas. They are mainly farmers who cultivate small areas in the vicinity of their homes. The standard of living is generally low. Leprosy control activities in the Nuba Mountains were started in 1936 when three colonies were established (Sudan, 1936). In 1937 a further four colonies were constructed and by 1948 the total number of patients in the colonies reached 1651. No further progress was achieved, and some missionaries who were responsible for these colonies were sent out of the country for political reasons in the early 1960's. A survey was carried out in a small area in the Southern Kordofan by Dr Ali Daw Al-Biet in 1966. The prevalence of leprosy was recorded as 56:1000. A more detailed survey was started by Dr Hussein Hassan, but unfortunately it was not completed.

In 1972 there were four colonies and one outpatient clinic in this area. The total number of patients in the colonies was 2751 (Table 1). Over 500 patients living in these colonies receive regular rations from the government; the rest live nearby and come for treatment only. All these patients are looked after by medical assistants and nurses, none of whom have had special training in leprosy.

TABLE 1

Leprosy patients in colonies in the Nuba mountains, 1972

Place	In-patients	Outpatients
Umdorien	200	225
Nyakma	137	1073
Kawda	95	716
Abri	82	116
Hieban	—	106

(b) *Southern Blue Nile and Southern Kassala Provinces*

In the 1940's a colony was constructed in Roseris, Southern Blue Nile, and some 140 patients now live there. It is perhaps enlightening to realise that most of these patients migrated from Kordofan, while others come from other Provinces including the Northern Province.

Apart from the Colony there are two highly endemic foci. One of them is in the Ingesana Hills, 50 miles south of Roseris. A sample leprosy survey carried out in this area in 1952 revealed that there are 500-600 patients in this area. Touring this area in 1972 and visiting most of its villages I had the impression that the number of patients cannot be less than 800. The other focus lies in another hilly area in the south, about 40 miles south west of Kurmak. Most of the patients live with their relatives, and very few report to Roseris Settlement.

In Southern Kassala there is a colony in Gedarif. The total number of patients reported in 1972 was 25, the same figure as reported in 1928, more than 40 years ago.

(c) *Southern Darfur*

Darfur is the Province which borders the Republic of Chad which is well known for its high endemic level for leprosy. There are two colonies, one in Zalinki started in 1933 with 24 patients, the other in Genena. The number of patients in these colonies in 1972 was 165 and 80 respectively. Apart from these colonies, no leprosy control activity has been undertaken in this area.

Leprosy in the Southern Region

The Region lies between latitude 10°N and 4°N. It extends from savannah in the north into tropical jungle in the south, and comprises mainly the three southern Provinces. It is inhabited by a jumble of tribes. The Nilotics who are mainly nomadic live in the north and central part, while the other tribes who are mainly farmers and hunters live in the south.

Leprosy work was started relatively early in this region, especially in the Zande area where it was carried out in connection with the well organized sleeping sickness campaign. It seems clear that the medical workers engaged in sleeping sickness control encountered many cases of leprosy.

In 1926 the number of patients was estimated to be 900-1000 for Equatoria Province, with a similar number for Bahr El Ghazal Province. By 1928 seven colonies were established and by 1930 the total number of patients reached 8000. In a survey carried out in 1952 in a population of 27,000 of the Moru tribes the prevalence was 44:1000; 10.2% of the cases were lepromatous in type.

TABLE 2

Leprosy patients in colonies in Bahr El-Ghazal province, 1972

Place	No. of patients
Wau (Agok)	130
Raga	80
Rumbek	240
Yirol	—
Tonj	—

Unfortunately this organised work was suddenly interrupted by the disturbances which broke out in the Southern Region. Some of the patients fled to neighbouring countries; those who remained were confined to the colonies. In Bahr El Ghazal Province there are now five colonies, with numbers of patients as shown in Table 2. In Upper Nile Province there are two colonies, one in Malek with 24 patients and the other in Maban area with 20 patients. In Equatoria Province there were 390 patients in Lui colony. After the Addis Ababa agreement a large leprosy settlement was established by the German CARITAS in Baria Band for leprosy patients returning to their own areas.

Conclusion

In conclusion, very little has been done in leprosy control. The present data are only approximate and may sometimes be misleading. For future planning more precise information is needed. Any help from World Health Organisation or any country would be welcomed, particularly in the field of statistics and case detection. This would enable us to plan on a sound foundation and look forward to a better future, and so overcome the gloomy past which characterized the leprosy work.

Acknowledgement

I am grateful to my colleague Dr Abdal Moniem Hassan Taha for his enthusiasm and for reading through the manuscript. My thanks are also due to Sister Christina for typing this paper.

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LEPROSY IN THE SUDAN

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With a limited national income and a surface area covering nearly a million square miles, the Sudan faces considerable problems in environmental health and the control of endemic diseases. Amongst the latter is leprosy, estimated by WHO to

affect 100,000 people, based on the 1966 population of 12,831,000. The population is now at least 16 millions, and in recent years some areas of high endemicity or hyperendemicity have been recorded by experienced observers. The leprosy control programme is still in the early stages of development, and factors such as poor roads and communications over vast distances, lack of transport, low population density, and limited funds for medical work generally have hindered progress in some provinces. Significant contributions are being made by Church Leprosy Relief, the Roman Catholic Church, the Swiss Government, and particularly by the German Leprosy Relief Organisation, who have started the construction of a leprosy training and demonstration centre in the south.

The leprosy control situation in the Sudan is described. Attention is drawn to the urgent need for some system of provincial and central registration of all patients, and for the collection of up-to-date statistical information not only from the 12 leprosaria, but also from all general hospitals and out-patient clinics in the country.

Leprosy in the Sudan has been described (Bechelli, 1970) as a serious public health problem, and in 1966, based on a population of 12,831,000 WHO estimated that there might be as many as 100,000 cases in the country.

A limited gross national income has resulted in small amounts of money being available for medical work (approximately 25 new pence per head per year), most of which – understandably – is absorbed by general preventive, curative and hospital services. The leprosy control situation has almost certainly been made even more difficult by the running down of missionary work in the North especially in Kordofan, and by the virtually complete withdrawal of missionaries from the South during disturbances in 1964. In recent years the Ministry of Health has welcomed aid from various outside agencies in their campaign against leprosy and the most significant development is that of the German Leprosy Relief Organization near Wau, in the southern Province of Bahr el Ghazal, where work has already started on a large leprosy training and demonstration centre. About 2 years ago, OXFAM received a request for practical help in the leprosy control programme, and the author was given the task of visiting the Sudan in order to obtain up-to-date information, with particular regard to statistics, training of personnel, transport, out-patient diagnosis and treatment, and the possibility of epidemiological studies.

Background Information

The Sudan is a vast, flat, hot country of clay plains, desert or duneland, with hills at the extremities. It is 10 times larger than Britain, with an area of nearly one million square miles – the largest country in Africa.

About 40% of the population are Arab, 20% central Nilotic, 10% Fur and other tribes of Darfur Province, and the rest Beja, Nubiyin and nilo-Hamitic. In the North, where over 2/3 of the people live, the feeling is Arab and Moslem, while in the three Southern Provinces of Bahr el Ghazal, Equatoria and Upper Nile, the people are Negroid or Nilotic, and there is a considerable ethnic, administrative and political boundary between the two regions. From about 2 million inhabitants at the beginning of the century, the estimated population is now over 16 millions; the pyramid of age distribution is broad-based, 5% being under the age of one year; 23% under five years; 50% under 19, 70% under 30, and only 1% over the age of 70. Until recently there were nine provinces; Blue Nile, Kordofan, Darfur, Kassala, Northern, Khartoum – all in the north; Bahr el Ghazal, Equatoria and Upper Nile in the south. A few months ago however, Kordofan, Kassala and

Blue Nile were all divided into two, and other subdivisions are in hand. Furthermore, the Ministry of Health has in some areas its own concept of Health Provinces, which do not necessarily correspond with political divisions. While certain roads leading out of Khartoum are good, most surfaces are of sand or mud, and liable to become totally impassable after the rains. There is a single track railway from Khartoum to the Northern Province; to the Red Sea; through Kordofan; to Darfur; into Blue Nile Province, and south to Wau in Bahr el Ghazal. It takes five days to get from Khartoum to Wau. Goods taken off ships in the Red Sea may take the better part of a year to get to the deep south.

Leprosy Statistics; Prevalence, Incidence

The enormous distances and problems of communication have made it difficult to collect accurate information on the total of registered patients in out-patient clinics or hospitals, though combined figures for in- and out-patients in leprosaria are available (see Table 1). Although the Vital and Health Statistics Division of

TABLE 1

Government leprosaria in the Sudan, April-May 1974, with approximated totals of in- and out-patients

Province	Provincial population[a]	Leprosarium ("colony")	Combined approximate total of in- and out-patients
Blue Nile	3,235,000	Roseiras	140
Darfur	1,735,000	Zalingi	165
		Genena	80
Equatoria	1,336,000	Juba (Luri)	700
		Bariabande	?
Bahr el Ghazal	1,463,000	Agok	214
		Rumbek	260
		Tong	174
		Raga	100
Kordofan	2,882,000	Om Durein	450
		Nyakma	1100
		Kawda	900
Approximate totals		12	4283

[a] Based on 1965 census. From 2 million people at the beginning of the century the figure rose to over 10 in 1956, to over 15 in 1969, and to at least 16 in 1974. The annual growth rate is 2.8%. Provincial populations for 1974 are not yet available.

the Ministry coordinates figures on leprosy for annual and other reports, it is not routinely notifiable (nor is tuberculosis). Based on a population of 12,831,000, WHO in 1966 estimated 100,000 patients for Sudan, i.e. about eight per thousand, and subsequent observers (Bechelli, 1962; Laviron, 1971) have seen no reason to reduce this figure. Laviron drew attention to high rates in the Nuba mountains, with prevalences of 25 per thousand in some places, and to figures of 14 per thousand in limited case-finding surveys in various villages. The map in Fig. 1 shows other areas where a high incidence of leprosy has been recorded in the

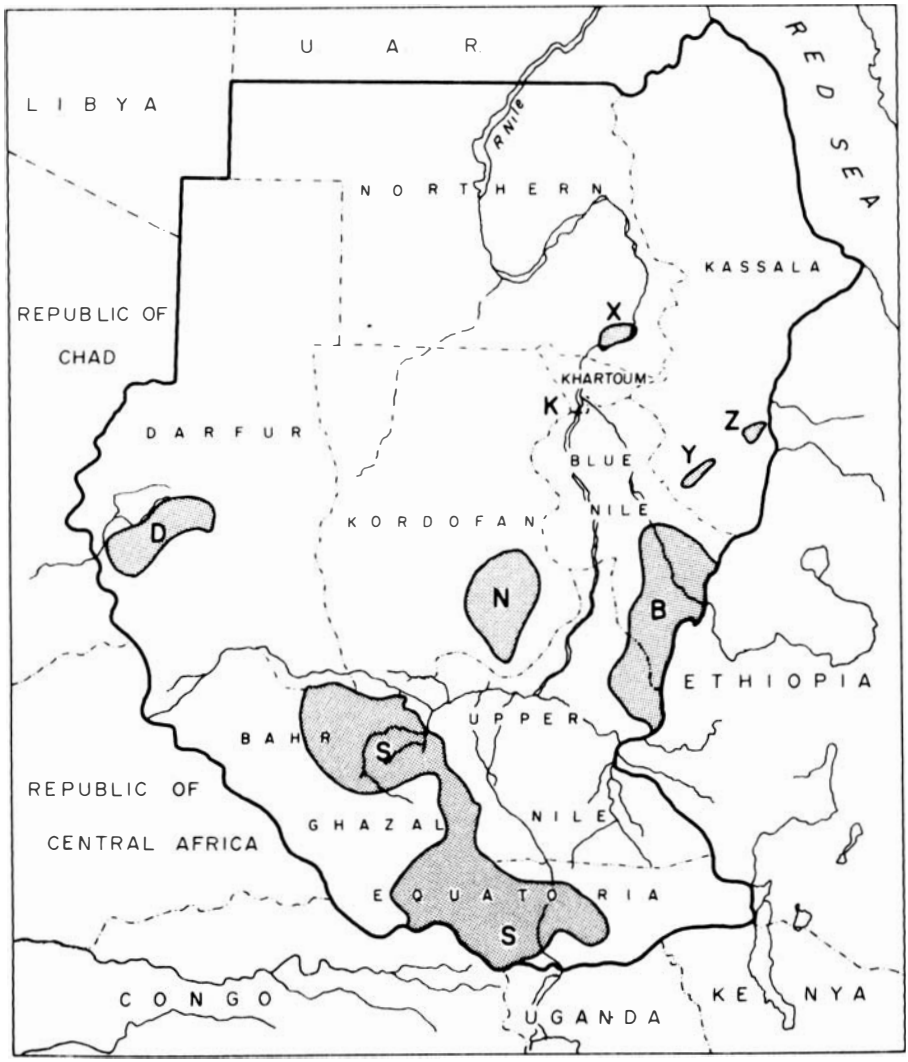

Fig. 1. The Sudan. (Department of Surveys, Khartoum; original scale 1:8 000 000). Nearly one million square miles in area, the country is bordered by—United Arab Republic, Red Sea, Ethiopia, Kenya, Uganda, Congo, Republic of Central Africa, Republic of Chad and Libya. K is Khartoum, the capital. The cross-hatching indicates areas where available evidence points to a significant incidence of leprosy. X, Y and Z are in Northern and Kassala Provinces, D in Darfur, B in Blue Nile, S and S in Bahr el Ghazal and Equatoria. N is the Nuba mountain area of Kordofan Province, where the highest incidence has so far been recorded.

past, or where new cases are continuing to occur. In common with experienced mission workers and all previous reports, doctors who have travelled the Sudan extensively agree that the most seriously affected area is in the Nuba Mountains of Kordofan Province (N).

Although the latest Annual Statistical Report (1971) from the Health Ministry gives figures mainly in the region of 1500 cases per year, it is the opinion of senior officials concerned with the interpretation of these returns that existing statistics are failing to reveal the true situation. This is mainly because a system of notification and registration of old and new patients has not yet been developed at district and provincial level, but also because too much emphasis has been given to in-patients in colonies, and their closely associated out-patients. Frequent movement of patients from one part of the country to another (for instance from Kordofan into Blue Nile, or from the southern province to Khartoum) has added to inaccuracies.

Structure of the Health Services in Relation to Leprosy Control

This has not changed substantially since the WHO assignments reports of Laviron (1971) and Wheate (1973). Virtually all districts are covered by hospitals and clinics which could effectively integrate leprosy out-patient diagnosis and treatment, but in practice there are serious problems related to low population density, bad roads and communications. Leprosy control is under the Rural Health and Endemic Disease Programmes in the Ministry of Health in Khartoum, where there is also a permanent WHO representative, and an office for the UNICEF combined smallpox-BCG inoculation programme. A National Plan for leprosy control was drawn up in 1972, after full discussion between the Ministry and all missionary and other agencies in the Sudan concerned with this disease. WHO has made a limited grant for consultancy, equipment and transport, and will supply a leprologist for the Leprosy Training and Demonstration Centre in the province of Bahr el Ghazal in the south, due to open in about two years from now. This centre, near Wau, the provincial capital, and only a few kilometres from the Government leprosarium of Agok, is at the stage of ground clearance at the time of writing. Despite some concern about rapidly mounting costs it could clearly develop as an important factor for the future of leprosy control in the Sudan. Apart from 48 hospital beds and a residence for semi-ambulatory patients, the plan includes facilities for out-patient treatment, physiotherapy, tailoring, carpentry, occupational therapy, repair and car workshop, and a leprosy assistant school. Residential accommodation for staff, students, guests and doctors is included. Other centres which have been constructed include (1) a 20-bed unit in the grounds of the Khartoum General Hospital, financed by the Swiss Government, now virtually completed. Although undecided as yet, it is thought likely that clinical responsibility will be shared between the dermatologists in an adjacent unit and Church Leprosy Relief; (2) a 20-bed unit at Rumbek in Equatoria in the south, a cooperation between the Catholic "Sudanaid" and the Government, where a group of sisters, trained at ALERT in Addis Ababa, are already at work. Apart from the wards, this unit will eventually include a doctor's house and out-patient clinic, with personnel and transport supplied by Sudanaid.

As regards general policy, the Ministry in Khartoum is insistent on priority for preventive, rural and environmental health programmes, and on their wish to follow WHO advice on leprosy control. While they have as yet to overcome many problems in the integration of leprosy work into general medical services, they have been able to follow up the oft-repeated policy (WHO, 1973) that "promotion of the training of general health personnel in leprosy control is receiving priority attention from WHO". A Medical Officer for Leprosy has been

appointed in the Ministry after a period of training in ALERT and in Uganda, three other Sudanese doctors have visited ALERT, and a surgeon has also studied there with a view to reconstructive surgery. In addition a number of mission sisters, one Catholic father, three male Sudanese nurses and a group of 10 medical assistants have also been trained either in ALERT, Karachi or Uganda.

Leprosy work in Khartoum and Omdurman

Church Leprosy Relief, in cooperation with the Abu Rouf out-patient clinics in Omdurman, now supervise the treatment of approximately 700 patients in Khartoum, Khartoum North and Omdurman. A Landrover is used to contact them at any convenient point or in "borrowed" clinic accommodation. They form a miscellaneous group, with a high percentage of deformity which has often attracted them to Khartoum and to professional begging. A surprising number originate from far-distant parts of the Sudan, including the deep south.

Provincial touring

Following discussion in Khartoum with the Ministry, WHO, UNICEF and mission personnel, visits were made to the Provinces of Kordofan, Blue Nile and Bahr el Ghazal with the main object of seeing out-patient facilities at first-hand while talking to doctors, medical assistants and others who might be handling leprosy patients, and paying visits to various leprosy colonies.

In all three provinces, there are adequate facilities for out-patient treatment, but distances from village to clinic either for the patient or the leprosy worker, together with the poor quality of roads, and the hazards of the rainy season make work difficult. Transport is in short supply; its integrated use for the prevention or treatment of several diseases at the same time has not yet been developed. In the south of Kordofan, 102 patients were examined in detail in the Government leprosarium of Om Durein. On a purely clinical assessment, 39 of these showed no evidence of clinical activity, had had long periods of in-patient treatment and were unclassifiable at the time of examination; 22 were lepromatous, obviously very long-standing, and apparently without any clinical activity; 17 had active lepromatous, 11 active borderline and 13 apparently inactive borderline disease. Serious disablement, including blindness, was common. From Om Durein in the south, via the district hospital at Kadugli, it is possible to make a loop through the Nuba Mountain area, returning to the more central district hospital at Dilling. This takes 13 hours and is mainly on roads which are bad in the dry season, impassable in the wet. At one remarkably remote point on this loop is the Government leprosarium of Nyakma, founded by the Sudan United Mission in 1939, and staffed by a group of expatriate missionaries until 1962, after which Government took over responsibility. Now to a considerable extent self-supporting and autonomous, figures are difficult to interpret in respect of (1) in-and out-patients (large numbers of the latter live in close proximity and their status is vague); (2) the numbers of healthy adults and children in or near the colony; (3) those who are officially entitled to "full" as against "supplementary" diet from the Government.

Laviron in 1970 found 258 out-patients as against 872 patients "in the settlement", but Ministry figures virtually reverse these; 137 in-patients and 1073 out-patients. A combined total of about 1100 may be near the mark. Many

patients have been in Nyakma for well over 10 years. Marriages are common; in 1970 there were 25 births and 81 healthy children, and today the figure for babies, infants and children may be nearer 200. The clinical situation here as regards classification, activity/inactivity, fitness for discharge to out-patient treatment, release from control, prevention and correction of deformity, needs detailed clarification, but it is clear that its remote situation, (it is completely cut off during the wet season) and the long periods of residence and marriages of so many patients will create peculiar problems. Clearly the correct yearly incidence of new cases and the lepromatous rate must be determined for this whole area as soon as possible. In Blue Nile Province, district hospitals and clinics were visited en route to Roseiras leprosarium where 114 patients were examined. Fifty eight showed no clinical activity, but were unclassifiable at the time of examination, 20 were long-standing, long-treated lepromatous patients without any clinical activity; 5 had well-settled, inactive borderline disease; 1 active tuberculoid; 9 active borderline and 21 active lepromatous. Deformity including blindness was widespread and severe in degree. In Bahr el Ghazal, the Government leprosarium of Agok, about 6 km from the provincial capital of Wau, and only a few kilometres from the German Leprosy Relief Organisation Project, had 112 patients available for clinical examination. Of these 63 showed no activity but were unclassifiable at the time of examination, 24 had apparently inactive lepromatous disease, and had been treated for periods as long as 10-15 years; 6 had inactive borderline disease; 15 active lepromatous and 4 active borderline. Again deformity of all kinds was widespread and advanced. Other leprosaria ("colonies") in the Sudan are shown in Table 1, where figures have been approximated between those in Ministry reports and other sources.

BCG inoculation in the Sudan

There is a combined smallpox-BCG campaign run by UNICEF, based on the Ministry of Health in Khartoum. Although the coverage for smallpox has been excellent (no known case in the country for over 15 months), that for BCG has not developed as planned, due to lack of vaccine and practical difficulties in giving both inoculations at the same time. About one million doses have been given in the six northern provinces, but in the three southern provinces the coverage was described as "negligible".

Discussion

Information gained during this visit confirms the impression of previous observers that there is indeed a serious leprosy problem in the Sudan, and that its magnitude and distribution are—almost urgently—in need of accurate clarification. The Ministry understands this well, one of their recent documents on the subject including the introductory statement: "Hence there is no accurate statistical data about the disease." In the Sudan this could be more important than usual, for its immense area of nearly one million square miles, coupled with limited resources in money and transport for leprosy work make it essential to give priority to areas of known high endemicity. Indeed a study of all previous reports, backed by the opinion of doctors who are experienced and widely travelled in the country,

suggests there are large, sparsely populated areas where it may be unrealistic to develop leprosy control services at all. However existing information from the known endemic foci, and from the 12 Government leprosaria is in need of much greater development as regards classification, activity/inactivity, length of treatment and disability grade. Intensive reassessments are needed to decide what proportion of leprosarium "in-patients" in fact need to stay any longer in an institution. At the same time out-patient treatment should be expanded so that the considerable costs of these colonies may be reduced. Plans are actively under discussion in Khartoum with the Ministry and Church Leprosy Relief for setting up a central Registry, which would involve the notification of every individual patient, with appropriate details. Reviewing the present leprosy control programme at the time or writing, it is difficult to see any more important step than the urgent development of this Registry so that the total picture may be defined. Incidental to this, information on the tribal and regional incidence of leprosy in the Sudan would surely be of epidemiological interest.

In the training of personnel it may well be that the total of those who have already been abroad for courses is adequate for the present needs, and that caution must be exercised to avoid the return of trainees, full of enthusiasm and new knowledge, to conditions which are—unavoidably—deficient in transport or such important details as clinical record cards, alternative drugs to Dapsone, drugs for the treatment of various forms of reaction, dressings for neuropathic ulceration and damage, plaster of Paris and footwear. It could well be that staff already trained will meet the needs satisfactorily until the opening of the training centre at Wau within the next few years. In the Government leprosaria however, it seems that day-to-day nursing, particularly in the field of prevention and correction of disabilities, together with social and physical rehabilitation, is difficult to meet. Should it be possible to reconcile with current political views, there is little doubt in the writer's mind that the introduction of small groups of medically trained mission sisters to some of these colonies would be of the greatest benefit.

In summary, the Sudan does indeed have a serious problem in leprosy, with particular difficulties related to its huge size, low population density, limited transport and poor roads. However the seeds of a constructive approach have been sown and if the impetus already shown by various foreign agencies can be followed up, matters may well improve. "One of the important conclusions to emerge from the Tenth International Leprosy Congress in Bergen, Norway in August, and marking the centennial of the discovery of *Myco. leprae,* was that, where an effective case-detection and case-holding programme has been developed, the total number of patients and the annual rate of detection of new cases has been reduced." (The Work of WHO, 1973.)

Acknowledgements

My thanks are due to OXFAM in Oxford and also to LEPRA in London, for asking me to undertake this tour. I am greatly indebted to the Ministry of Health and to Sister Hazel Caren of Church Leprosy Relief in Khartoum for so much advance planning of the itinerary. My wife Josephine painstakingly recorded almost all the information on which this report is based. This work is supported by grants from the Medical Research Council and the British Leprosy Relief Organisation (LEPRA).

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*These are numbered WHO assignment reports, and should not be regarded as publications.

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Field Workers' Forum

THE RECOGNITION AND MANAGEMENT OF NERVE DAMAGE UNDER FIELD CONDITIONS

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Introduction

Recognition that nerves are being damaged may not be easy, because it can occur without causing pain. It is often overlooked by leprosy workers, and may even be overlooked by the patients themselves. Each time the patient comes for treatment the field worker should:

(1) Test for neuritis by examining the important nerve trunks for tenderness;

(2) Test for nerve damage by:

(a) questioning the patient about his general health. Most patients who are developing nerve damage also have other symptoms such as vague aches and pains, mild fever, burning or numbness of the skin, or simply do not feel well.

(b) Examining the face, hands and feet for signs of weakness of the muscles.

Correct management of nerve damage and neuritis is most important. It is the one thing that can prevent the development of disability.

Recognition

We shall consider:
1. Symptoms
2. Signs
3. A Severity Scale
4. An "At Risk" Register

1. *Symptoms*

(a) *Pain.* Patients with nerve damage often complain of pain of the nerves or joints. This pain may be severe enough to prevent sleep or work. Pain may also be very mild. Some patients are strong and used to pain. They expect to have pain with leprosy and may not complain unless asked about it.

(b) *Numbness.* Patients often complain of numbness. It is important to be certain that they really mean loss of feeling. Good records of the extent of loss of

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feeling at the time the patient is first seen are very important; without them it is impossible to tell whether the loss of feeling is becoming greater or not. Only if it is becoming greater is it evidence of nerve damage.

(c) *Burning feeling in the skin.* This may be the first sign that nerves are being damaged.

(d) *General symptoms.* Many patients developing nerve damage do not feel well, and may have mild fever.

(e) Very commonly nerve damage occurs when there is also reaction developing in skin lesions.

2. *Signs*

(a) *Signs in the nerve trunk itself.* In cases of neuritis, nerve trunks will be enlarged, tender and may be hard. Feel these nerves gently, using the pulp of the fingers and not the extreme tip. The ulnar nerve can only be examined properly with the patient's elbow bent, and the peroneal nerve with the patient sitting down. Watch the patient's face as you feel the nerve. Compare right and left sides as this will help you to estimate size. You can only get to know the size, tenderness and hardness of normal nerves by examining many, many cases. Practise this often. But remember that nerves can be damaged even if they are not painful or tender.

(b) *Loss of feeling.* Dryness in hand or foot is a useful guide to loss of feeling, as dryness and loss of feeling usually go together. The following test has been found to be of practical value for hands and feet:

> With the patient's eyes shut, use the point of a ball-point pen or pencil and touch the palm of the hand or sole of the foot firmly. If the patient has protective sensation he will feel this touch and be able to point exactly to the spot where he was touched. If his sensation is seriously diminished he will miss the mark. Record in centimetres the distance by which he misses.

Sensation in the eye must be tested with a wisp of clean cotton wool.

(c) *Weakness.* Simple tests for weakness include:

(i) Outward movement of the little finger.
(ii) Pinch between thumb and little finger.
(iii) Dorsi-flexion of foot against resistance.
(iv) Attempted closure of the eyes.

(d) *Swelling.* Swelling (oedema) may be found together with nerve damage. If oedema develops first, it is a warning that nerve damage may soon follow.

(e) *Signs of reaction in skin lesions* often occur when nerves are being damaged.

3. *A Severity Scale*

Always record the severity of the patient's symptoms and signs according to these definitions:

(a) *Pain.* Mild pain–discomfort not sufficient to interfere with work or sleep. Severe pain–the patient is unwilling to move the limb, and sleeping is disturbed.

(b) *Tenderness.* Mild tenderness–shown by firm pressure on the nerve trunk. Severe tenderness–shown by light touch on the nerve and by tenderness in the skin overlying the nerve.

(c) *Enlargement.* Try to estimate the size of the nerve in millimetres.

(d) *Hardness.* Nerves may be:

(i) Normal—that is, a little bit soft so that you feel you can squeeze them rather like microcellular rubber used in shoes.

(ii) Firm—like very hard rubber.

(iii) Hard—as hard as bone or marble.

4. *"At Risk" Register*

Use some simple record to draw your attention to cases at risk of getting neuritis. This may be done by putting a red star, for example, against the patient's name in your treatment register or on the top left-hand corner of his card, if the card is used every time he comes for treatment. Cases at risk include:

Active cases in the borderline group.

Lepromatous cases who have had ENL (Type 2 Reaction).

Management

It is worthwhile to remember that not *all* cases of neuritis in leprosy patients are due to leprosy. Types of polyneuropathy which may mimic leprosy neuritis include:—

1. Vitamine B_1 (thiamine) deficiency which may be seen in alcoholics and in association with beri-beri or diabetes.
2. Vitamine B_6 (pyridoxine) deficiency, or over excretion as in patients on isoniazid.
3. Other toxic neuropathies associated with drugs or poisons e.g., heavy metals, including pesticides containing arsenic.
4. Infectious neuropathies including those associated with diphtheria and the Guillain-Barré syndrome.

The cause of mononeuropathies is usually local and obvious but the carpel tunnel syndrome, ulnar or common peroneal neuritis due to trauma and lateral fermoral cutaneous nerve entrapment may also mimic neuritis due to leprosy and require appropriate treatment.

Management of neuritis due to leprosy depends upon the classification of the case. We shall consider:

1. Borderline and Tuberculoid cases under treatment.
2. Lepromatous cases under treatment.
3. Cases not under treatment.

1. *Borderline and Tuberculoid Cases under Treatment*

(a) *Mild cases.* i.e. mild rheumatic pain, mild tenderness alone, or tenderness with swelling.

(i) Aspirin two tablets three times a day. Ephedrine 7 mg three times a day. Continue anti-leprosy treatment.

(ii) Tell the patient to report immediately if pain increases or loss of function occurs.

(iii) Put the patient on your "At Risk" register.

(b) *Severe cases.* i.e. severe pain and tenderness with swelling and often acute loss of function.

(i) Refer the patient immediately to hospital or a centre where steroids are available.

(ii) If permitted to do so, give 30 mg Prednisolone in a single dose before the patient is sent to hospital.
(iii) Splint the limb if possible, or use a sling for the arm.
(iv) Make careful records of your findings and send them with patient.

(c) *Late discovery of pain or loss of function.* If loss of function or pain has been overlooked for some reason, hospital referral is still worthwhile in all Borderline/Lepromatous cases up to six months after it occurred. In Borderline/Tuberculoid cases it is probably only worthwhile up to about three months after it has occurred.

2. *Lepromatous Cases Under Treatment*

(a) *Neuritis associated with ENL of the skin.* See Leprosy Review "Field Workers' Forum", December 1974.

(b) *Neuritis not associated with ENL in the skin.* Treat in the same way as borderline and tuberculoid cases (see section on Management, 1(a) or (b) according to severity). But do not give Prednisolone for pain unless there is also loss of function of the nerve.

(c) *Gradual loss of function during treatment.* This sometimes happens in lepromatous cases when there are no painful or tender nerves. We know of no effective treatment for this process.

3. *Cases not under Treatment*

Nerve damage and neuritis hardly ever need specific treatment in patients with untreated lepromatous leprosy. But this is not so in borderline and tuberculoid cases.

(a) *Borderline and Tuberculoid cases not previously diagnosed.* Neuritis and loss of function are often the reasons for patients coming for diagnosis. They should be placed on anti-leprosy treatment and treated for nerve damage as under Management 1(a) or (b) (according to severity).

(b) *Borderline and Tuberculoid Relapse Cases.* Nerve damage is often an early sign of relapse and may appear before skin lesions. If there is any doubt that the leprosy has relapsed such cases should be referred to hospital for assessment. If however, it is clear that relapse has occurred, restart treatment and treat nerve damage as under Management 1 (a) or (b) (according to severity).

Health Education

This is a subject in itself, and will be considered in a later article in this series. All that need be said here is that, even if there is permanent nerve damage, severe deformity can be prevented by simple exercises and skin care. These exercises should be known by every field worker, and taught to all patients whose nerves are damaged and who may therefore develop deformities.

Conclusion

Recognition and correct management of nerve damage is well worth while. Permanent nerve damage and deformity can be prevented in most cases if it is recognized early and correct treatment is given immediately. Even if nerve damage is permanent, severe deformity can be prevented by exercises and education.

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Letters to the Editor

Dapsone Dosage and Drug Resistance

Dr Browne's recent contribution in the Field Workers' Forum (*Leprosy Review* Vol. 45, 276) on the subject of drug resistance in leprosy gives practical and helpful advice concerning the dangers of dapsone resistance. The dilemma is clearly outlined that one needs to consider lower dosage for tuberculoid patients because of the danger of nerve damage, but at the same time be sure that adequate dapsone is given to suppress bacterial growth in patients with lepromatous leprosy. Obviously the type of leprosy must be correctly determined, and this basic ability is essential in every worker who aspires to treat leprosy patients.

Problems arose in the past because we erred in treating tuberculoid leprosy too enthusiastically, and lepromatous leprosy too conservatively, on the assumption that because it was the serious form of the disease greater caution was necessary. In fact it has been proved that low dose dapsone therapy suffices in patients with tuberculoid leprosy to assist the immune process and control the multiplication of bacilli, but in lepromatous leprosy the battle depends on the effectiveness of the drug, since host immunity is too low to control the infection alone. Now that this has been clarified, can we not develop a treatment schedule that will apply to all situations?

In such a schedule three variables need to be taken into consideration:

(a) The body weight of the patient.
(b) The type of leprosy.
(c) Complications arising in the course of treatment.

At a recent Leprosy Conference of the English speaking countries in West Africa, a committee was asked to work on a dapsone dosage scheme which we would agree would be the best, and yet simple, so that it would be practical for out-patient programmes and for paramedical staff to supervise. This committee included Drs Ross, Wheate, Odoghe, Beniccio, Pfaltzgraff and Professor Schaller. Treatment *on a daily basis* was strongly recommended, and the following routine schedule was agreed upon.

1. Dapsone treatment to be given daily, using 25 and 50 mg tablets only.
2. For all types of case:

Adults	Initial dose	25 mg daily
	After three months	50 mg daily
	After six months in BL/LL cases only, 100 mg daily.	
Children	Under the age of five years, the diagnosis to be confirmed by an experienced person, preferably M.D. and a maintenance dose of 2 mg/kg/day given.	
	Age 5-12 years; a standard daily dose of 25 mg, both for initial treatment and maintenance, in all types of leprosy.	

This proposed scheme offers three advantages:

1. It makes allowance for the problem of neuritis in tuberculoid leprosy, and yet provides an adequate dose for the control of lepromatous disease.
2. The scheme is simple to follow, and can easily be remembered by auxiliary staff.
3. It allows for an average dose of 2 mg/kg daily in lepromatous patients, in whom this dose is essential.

At this stage in the development of adequate dosages to treat leprosy in control programmes, it seems to me imperative to develop a treatment regime that can be universally accepted. Could not the above suggestions serve as a starting point for discussion on this subject?

If such a scheme as this is to be used more extensively, it will be important for UNICEF to supply tablets of 25 and 50 mg dapsone as routine, distinctively coloured. The 100 mg tablet could become redundant.

Since it is only the complications of leprosy that lead to disability, it is sometimes more important to control the complications than to treat the disease. Whenever there is danger of the development of permanent disability, whether as the result of neuritis or iritis, the patient should at once be placed under experienced and expert medical care.

To refer back again to Dr Browne's notes; I question the validity of a maintenance dose of half the therapeutic dose for lepromatous patients after arrest. May this not give a level of dapsone concentration in the blood below that necessary to provide bacteriostasis?

Finally, how long must a patient with dapsone resistant bacilli be treated with clofazamine before treatment can be stopped or resumed with dapsone? We have tried to start dapsone again at a level of 600 mg per week after two years treatment with clofazamine, but after four years on dapsone it is evident that a dapsone resistant clone of bacilli has again appeared. A report of the experiences of others in this regard will be welcome.

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Further contributions on this subject will be welcomed. *Ed.*

COMMENT BY DR GORDON ELLARD

Dr Davey has invited me to respond to Dr Pfaltzgraff's letter concerning dapsone dosage and drug resistance. The most important point I would like to make is concerning the last paragraph of the letter in which Dr Pfaltzgraff asks how long a patient with dapsone-resistant bacilli must be treated with clofazimine before treatment can either be stopped or else resumed with dapsone. My response would be that if a lepromatous patient relapses with bacilli that have been shown by the foot-pad technique to be fully resistant to dapsone (i.e. they multiply in mice fed 0.01% dapsone in the diet) and the only other antileprosy drug available is clofazimine, then treatment with clofazimine should be continued until it is believed the patient has been cured.

The reason for advocating this approach is that dapsone resistance appears to be a stable characteristic of dapsone-resistant *Myco. leprae*. Thus dapsone-resistant strains of *Myco. leprae* can be successfully passaged for many years in untreated mice (Shepard *et al.*, 1969). As a consequence one must expect that a patient with fully dapsone-resistant *Myco. leprae* will always remain unresponsive to dapsone treatment.

Unfortunately, the length of treatment required to cure lepromatous patients with clofazimine has still to be established. It is almost certainly many years since the initial rates of fall in the numbers of viable *Myco. leprae* when such patients are treated with dapsone or clofazimine are similar (Pettit and Rees, 1966; Pettit *et al.*, 1967; Levy *et al.*, 1972) and it is clear that considerably more than 10 years of dapsone treatment must be given before hopes of curing all patients can be entertained (Waters *et al.*, 1974).

The results described by Dr Pfaltzgraff, when a patient with dapsone-resistant leprosy was treated for two years with clofazimine and then switched to dapsone, are therefore readily understood. Clearly significant numbers of viable dapsone-resistant *Myco. leprae* still remained after two years clofazimine treatment, which were then able to multiply again when treatment was changed to dapsone until four years later they resulted in the patient relapsing bacteriologically.

Although clofazimine-resistant strains of *Myco. leprae* have yet to be isolated, the possiblity that long-term treatment with clofazimine alone may result in lepromatous patients eventually relapsing with drug-resistant *Myco. leprae* must still be seriously considered. For reasons discussed more fully in the Editorial of this issue, I would therefore recommend that every effort should be made to treat patients with dapsone-resistant leprosy with combinations of two other antileprosy drugs. In Sungei Buloh such patients are treated with combinations of clofazimine, rifampicin or thiambutosine (Helmy *et al.*, 1973). The potential value of even as little as a week of rifampicin treatment in reducing the likelihood of lepromatous patients relapsing with drug-resistant strains of *Myco. leprae* has been discussed elsewhere (Ellard, 1975). Thereafter thiambutosine or thiacetazone might be used as long-term companion drugs.

In most countries resources are simply not available for establishing by the mouse foot-pad technique whether or not patients are infected with dapsone-resistant *Myco. leprae*, and even when the method can be carried out it would normally take the best part of a year for the results to become available. In such a situation I would recommend that lepromatous patients, who have been treated with dapsone for over five years and who are clearly relapsing clinically and bacteriologically despite fully supervised dapsone treatment (Pettit *et al.*, 1969), should continue treatment with high dosage dapsone (100 mg per day) and that this treatment should be supplemented with clofazimine and another companion drug for as long as seems reasonably possible. In this way patients whose bacilli are partially sensitive to dapsone (Pearson *et al.*, 1968; Shepard *et al.*, 1966) would benefit from the therapeutic activity of all three drugs and relapse due to the appearance of drug-resistant strains of *Myco. leprae* would be extremely unlikely.

Finally, I should like to make two further points concerning Dr Pfaltzgraff's letter. Firstly, I would suggest that the chances of lepromatous patients eventually relapsing with dapsone-resistant leprosy would be significantly reduced (and without any concomitant increase in the incidence of *erythema nodosum leprosum*) if treatment was begun immediately with 100 mg dapsone daily,

instead of after six months daily treatment with 25-50 mg dapsone as in the proposed dosage schedule. Secondly, I would emphasize that doses of as little as 1 mg dapsone a day are effective in preventing the multiplication of *fully sensitive* strains of *Myco. leprae.* The rationale for giving the highest doses of dapsone that are well tolerated, is the hope that in this way the growth can be prevented of the small numbers of naturally dapsone-resistant *Myco. leprae* that are presumed to be present in the enormous populations harboured by lepromatous patients prior to treatment.

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The Broach Biopsy Technique in Infective Granulomatous Diseases

It is sometimes difficult to obtain full patient co-operation in taking pathological specimens in leprosy using Wade's scraped incision technique. This applies especially to children who are often terrified at the sight of a doctor and a scalpel. A simple technique is available which largely avoids these problems and at the same time provides a reliable pathological specimen. An endodontic broach is used by dentists to remove the nerve from the apical canal (Fig. 1). It consists of a disposable fine tempered steel needle with a screw thread or barbs on one end.

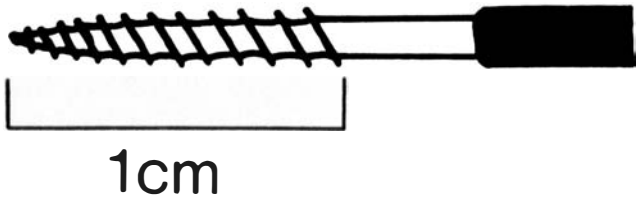

Fig. 1. Endodontic broach. (× 5.)

The needle is inserted into the centre of a granulomatous lesion, given a half-turn then pulled out, at the same time pressing on the skin near the puncture point to prevent "tenting" of the skin. A smear is made on a glass slide in a very small drop of saline and then stained with a modified Ziehl-Neelsen technique for *Myco. leprae.*

Good specimens were obtained in two patients with lepromatous leprosy. In the second patient smears were made from the same nodules at three different sites using both the scraped incision and the broach biopsy techniques. All smears were positive with slightly more material being obtained with the standard technique (Figs 2 and 3).

The broach biopsy was first suggested by Gremliza (1956) for the diagnosis of cutaneous leishmaniasis. Further trials in an area where leishmaniasis is endemic fully confirmed the value of the technique for use in field work and screening clinics in this condition (Griffiths and Dutz, 1975).

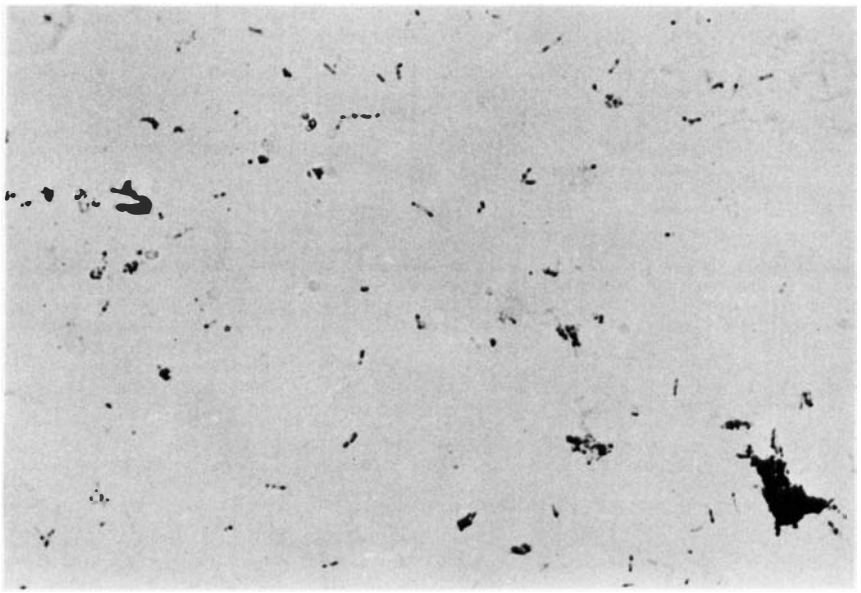

Fig. 2. Ziehl-Neelsen stain of tissue smear using broach. (× oil immersion.)

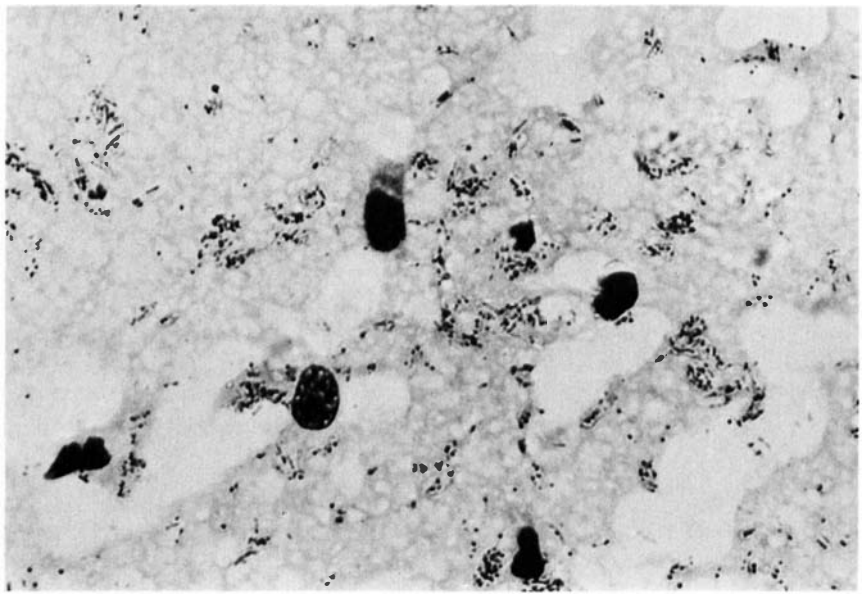

Fig. 3. Ziehl-Neelsen stain of tissue smear using scraped skin incision. (× oil immersion.)

The rapidity, simplicity and the cheapness of the broach biopsy method may make it a useful addition to the techniques available to leprologists.

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Lepr. Rev. (1975) **46**, 241

Book Review

The Diagnosis and Management of Early Leprosy, by S. G. Browne. London: Leprosy Mission. 35 pp.

This little book, intended for general medical practitioners who may encounter leprosy in their practice is one of a series on "Leprosy Today" being published by the Leprosy Mission for free distribution. Written with great clarity, its 35 pages distil the experience and wisdom for which Dr Browne is renowned. The emphasis throughout is on *early* leprosy, the recognition of which is described comprehensively and in detail, while an important section of the book describes the management of leprosy in its early stages. There are four pages of coloured photographs illustrating early leprosy lesions.

This book should be in the hands of every doctor working in countries where English is understood and leprosy is endemic. It is available gratis from the Leprosy Mission, 50 Portland Place, London W1N 3DG.

T. F. DAVEY

Lepr. Rev. (1975) **46**, 243-253

Abstracts

1. BECHELLI, M. L., KYAW LWIN, GALLEGO GARBAJOSA, P., MG MG GYI, UEMURA, K., SUNDARESAN, T., TAMONDONG, C., MATEJKA, M., SANSARRICQ, H. & WALTER, J. **BCG vaccination of children against leprosy: nine-year findings of the controlled WHO trial in Burma.** *Bull. Wld Hlth Org.* 1974, v. 51, 93.

The leprosy incidence rates so far in the vaccinated and unvaccinated children aged 5-9 and 10-14 years are similar. The BCG-vaccinated children aged 0-4 years at intake had an incidence rate lower than that of children in the control group. BCG vaccination did not protect household contacts or children aged 5-14 years not exposed in the household, and did not influence the distribution of the forms of leprosy in the cases detected. The lepromin reaction in relation to the age at intake was consistently stronger in the vaccinated children than in those of the control group; the younger the age group the more pronounced was the difference, which was only slight in the age group 10-14 years at intake. If the results of the late lepromin reaction are related to the age at onset (when the children are older than at intake), the differences between the BCG and the control groups tend to decrease. It does not seem that the BCG-vaccinated children suffer from a less serious form of leprosy than the nonvaccinated children (most of them nonreactors to tuberculin).

Authors' Summary

2. PALANDE, D. D. **A review of 23 operations on the ulnar nerve on leprous neuritis.** *J. Bone & Joint Surg.* 1973, v. 55-A, 1457.

Ulnar neurolysis and transposition operations were undertaken on 23 patients with leprous neuritis producing intractable pain, including seven with nerve abscess. The pain was relieved in all cases. Recovery of sensory and motor function varied with the type and duration of neuritic involvement. The results show that meticulous surgery on the diseased ulnar nerve in such patients can be done without damaging the nerve, and undertaken early may be a way to diminish the incidence of irreparable nerve damage.

T. F. Davey

The following Abstracts are reprinted, with permission, from *Tropical Diseases Bulletin,* January to April 1975.

3. WLD HLTH STATIST. REP., 1974, v. 27, No. 6, 234-6. **Leprosy.** [In English and French.]

Figures are given, where available, showing the numbers of cases of leprosy reported monthly in 1972 and 1973 in some 60 countries in Africa, the Americas, Asia, Europe, and Oceania.

4. SAINT-ANDRÉ, P. & CLASTRE, J. L. Une enquête sondage d'évaluation de la campagne contre la lèpre dans une zone de grande forêt en Côte-d'Ivoire (Région de Danané). [**A pilot evaluation enquiry into a leprosy campaign in an area of dense forest in the Ivory Coast (Danané district).**] *Méd. Trop.,* 1974, v. 34, No. 3, 361-5. English summary.

This brief paper summarizes the findings of a pilot survey designed to evaluate the results of a leprosy control programme in typical groups of small villages scattered in an area of dense

tropical forest. The whole population numbered about 18,000; the prevalence of leprosy was low, and a very low proportion of patients suffered from the lepromatous form. Total coverage was believed to have been achieved.

The authors consider that the routine treatment – fortnightly injections of suspensions of dapsone – resulted in clinical arrest in 65% of patients in 3 to 4 years, despite an undisclosed proportion making 50% of clinic attendances or less. The prevalence of leprosy has fallen to 5 per 1000. The authors recommend that doctors should release patients from treatment with greater readiness and, in such an area, that the leprosy programme should be combined with a campaign against other prevailing diseases, such as onchocerciasis.

S. G. Browne

5. MYRVANG, B. **Immune responsiveness to *Mycobacterium leprae* of healthy humans. Application of the leucocyte migration inhibition test.** *Acta Path. Microbiol. Scand. Sect. B,* 1974, v. 82B, No. 5, 707-14.

"Immune responsiveness to *Mycobacterium leprae* was studied, by the method of leucocyte migration inhibition, in 90 healthy adults allocated into four groups according to previous contact with leprosy patients. Groups working or living in close relationship with leprosy patients responded significantly more strongly to *Myco. leprae* than a group without such contact. With a selected concentration of *Myco. leprae* 71.2% of medical attendants dealing with leprosy patients, 22.2% of administrative staff of a leprosy hospital, and 50% of household contacts of leprosy patients showed migration indices <0.800, but none of the group without known contact with leprosy patients showed indices below the threshold value. Since the inhibition of migration to BCG was similar in all groups, and no evidence was found that other mycobacteria had provoked the positive responses elicited by *Myco. leprae,* the above figures appear to represent individuals immunologically stimulated with *Myco. leprae* itself. The study therefore, showed that the method of leucocyte migration inhibition may be used as an assay for specific detection and enumeration of immune responses mounted by *Myco. leprae.* The results lend strong support to the view that leprosy bacilli are frequently transmitted from patients to contacts. The introduction of *Myco. leprae* into the human body is, however, rarely accompanied by development of clinical signs of leprosy."

6. KAHN, P. & SCOTT, T. **The pathology of a radial nerve biopsy in leprosy: light and electron microscopy.** *J. Path.,* 1974, v. 114, No. 2, 97-100.

"Light and electron microscopy of a radial nerve biopsy in a patient with longstanding leprosy and treated for four years, shows that in the nerve the end result of prolonged infection is loss of nerve fibres, severe endoneural fibrosis, and lamination of Schwann cell processes and collagen. These appearances resemble the 'onion bulb' whorls seen in other chronic peripheral neuropathies. Several bacilli and fragments of degenerate organisms were deomonstrated, which illustrates the difficulty of eradicating reservoirs of organisms which may persist in spite of prolonged treatment."

7. DASTUR, D. K. & DABHOLKAR, A. S. **Histochemistry of leprous nerves and skin lesions: acid phosphatase.** *J. Path.,* 1974, v. 113, No. 2, 69-77.

The occurrence of acid phosphatase in nerves in leprosy, not previously investigated, was found to be similar to that in skin lesions. In tuberculoid nerves enzyme activity showed three phases: almost none in the normal state, increased activity in the stage of early degeneration, and again none in the advanced stage. The situation in lepromatous nerves was probably similar. The enzyme was thought to be in the Schwann cell cytoplasm as well as in macrophages. Acid

phosphatase appears to be a reliable marker of lysosomal activity but does not by itself control bacillary multiplication.

D. S. Ridley

8. SAINT-ANDRÉ, P., FERAL, J., BUENO NUMEZ, A. M., GIRAUDEAU, P. & CISSE, B. Le traitement de l'érythème noueux lépreux (ENL) par le chloramphénicol. [**The treatment of erythema nodosum leprosum with chloramphenicol.**] *Afr. Méd.*, 1973, v. 12, No. 115, 871-8.

The authors treated with chloramphenicol 31 African patients suffering from clinically severe (22) or moderate (8) grades of erythema nodosum leprosum (ENL), and one patient with an acute peripheral neuritis. After careful pathological assessment, the patients were given 1 g of the drug three times a day; three-quarters took the drug orally and the remainder received it intramuscularly.

In patients suffering from severe ENL, either long-standing or recurrent, the raised temperature returned to normal within a week, and the skin lesions disappeared within 12 days in all patients and within eight days in a third. The level of C-reactive protein, which had been considerably raised in all patients, fell to zero within 18 days in all patients, and within 11 days in 60%.

In patients with less severe forms of ENL, a similar rapidity of disappearance of signs and pathological accompaniments was noted in some, but not in those patients suffering from a persistence of fewer ENL lesions.

The authors consider that chloramphenicol must now be reckoned as inferior only to thalidomide in the control of ENL, although relapse occurred in 30% of patients between 15 days and 4 months.

The mode of action of the drug is discussed in some detail, and the intriguing possibility that, in some instances at least, reaction may be precipitated by the presence of staphylococci in the urinary tract or elsewhere. The authors suggest that chloramphenicol may act on the antibodies that represent one of the components of the immune complex responsible for the triggering of the "reaction". Whatever the explanation, the treatment of a notoriously refractory complication of lepromatous leprosy by means of chloramphenicol deserves further investigation.

S. G. Browne

9. ANTIA, N. H. & BUNDEALLY, A. E. **Prolonged release of 4,4′-diamino-diphenylsulphone (DDS) by incorporation in silicone rubber.** *Int. J. Lepr.*, 1974, v. 42, No. 1, 58-62.

"Prolonged release of DDS by incorporation into silastic RTV sheets has been demonstrated in *in vitro* and *in vivo* studies in rabbits up to a period of 150 days. This is a preliminary report of a continuing study."

10. BEAMAN, B. L., KIM, K. S., LANÉELLE, M. A. & BARKSDALE, L. **Chemical characterization of organisms isolated from leprosy patients.** *J. Bact.*, 1974, v. 117, No. 3, 1320-29.

Cell wall preparations from 13 leprosy-derived bacteria were analysed for carbohydrate, lipid and amino acid composition. These were compared with analyses of a characteristic species of *Corynebacterium, Mycobacterium* and *Propionibacterium.* All but one of the leprosy-derived bacteria could be assigned to one of these genera on this basis and the authors note that the characteristics of freshly isolated "leprosy bacilli" reported in the literature are encompassed by a combination of these genera but not by one alone. A mixed aetiology of leprosy in which mycobacteria and propionibacteria function as "helper bacteria" in the development of globi from spheroidal bodies is discussed.

S. Fletcher

11. SHAO, J. **Affinity of *Myco. leprae* to lymphocytes of leprosy patients in vitro.** *Dar es Salaam Med. J.*, 1973, v. 5, No. 1, 27-8.

"The adherence of *Mycobacterium leprae* to lymphocytes from patients with tuberculoid and lepromatous leprosy has been studied. The two groups were studied simultaneously.

"While lymphocytes from nine tuberculoid patients showed very high adherence property to the *Mycobacterium leprae,* there was an obvious diminished affinity for the leprae among the lymphocytes from nine lepromatous patients.

"It is concluded that lepromatous patients have a diminished number of circulating lymphocytes that have antigenic receptors for *Mycobacterium leprae.*"

12. IMAEDA, T. **Growth inhibitory activity of deoxyribonucleic acid-containing factor(s) isolated from lepromatous lesions.** *Infection & Immunity,* 1974, v. 10, No. 4, 957-9.

"Deoxyribonucleic acid-containing factor(s) isolated from *Mycobacterium leprae* suspensions obtained from lepromas of nine patients showed growth inhibitory activity against *Micrococcus* and both orange-red-pigmented and coccoid mutants of mycobacteria. No growth inhibition was observed for parent mycobacterial species, *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis,* and *Staphylococcus epidermidis.*"

13. LIM, S. D., KIM, W. S., KIM, C. S., GOOD, R. A. & PARK, B. H. **NBT responses of neutrophils and monocytes in leprosy.** *Int. J. Lepr.*, 1974, v. 42, No. 2, 150-53.

"A role of cellular defense against infection of *Mycobacterium leprae* was studied with 36 leprosy patients. Using the NBT test, we found no significant difference in the proportion and absolute number of NBT positive neutrophils. However, these indices were markedly increased in the monocytes. Thus our results confirm that the monocytes are of prime importance in the defense against *Mycobacterium leprae,* but neutrophils are not. Neutrophils, however, do respond well against test endotoxin in this disease."

14. HAN, S. H., WEISER, R. S., WANG, J. J., TSAI, L. C. & LIN, P. P. **The behaviour of leprous lymphocytes and macrophages in the macrophage migration-inhibition test.** *Int. J. Lepr.*, 1974, v. 42, No. 2, 186-92.

"The bahavior of leprous lymphocytes and macrophages in the cell-mediated immune response to the specific antigens of leprolin was studied *in vitro* by the macrophage migration-inhibition test using a pure human cell system and a mixed cell system comprised of human lymphocytes and guinea pig macrophages. In the presence of leprolin, the migration of normal guinea pig macrophages was inhibited in the presence of tuberculoid lymphocytes but not in the presence of lepromatous or normal lymphocytes. In the presence of leprolin and tuberculoid lymphocytes, macrophages from tuberculoid, lepromatous and normal subjects showed similar degrees of migration inhibition. Whereas the migration of lepromatous macrophages was not inhibited in the presence of leprolin and either normal or lepromatous lymphocytes, the migration of tuberculoid macrophages in the presence of leprolin and lepromatous lymphocytes was inhibited to a slight but singificant degree.

"The results indicate that the capacity of lepromatous lymphocytes to respond to leprolin with the production of MIF is severely if not totally impaired but that the capacity of lepromatous macrophages to respond to MIF is normal. They also indicated that tuberculoid lymphocytes are sensitive to leprolin and can produce MIF in its presence."

15. AZULAY, R. D., SILVA, N. C., ZEO, A., PORTELA, A. B., FRANCA, J. C. B. & PELUSO, L. L. **The antileprotic action of clofazimine (B 663, G 30 320, Lamprene).** *Int. J. Lepr.,* 1974, v. 42, No. 1, 13-18.

Twenty patients in Rio de Janeiro were treated for 1-2 years with clofazimine (Lamprene; B 663) in a dosage of 100-200 mg daily. All were suffering from lepromatous leprosy and five had not been treated previously. The only side-effects were pigmentation and dryness of the skin, and mild indigestion. Results were good and the incidence of lepra reaction was low.

W. H. Jopling

16. ENNA, C. D. & JACOBSON, R. R. **A clinical assessment of neurolysis for leprous involvement of the ulnar nerve.** *Int. J. Lepr.,* 1974, v. 42, No. 2, 162-4.

"Neurolysis with or without transposition of the ulnar nerve was performed 103 times on 63 patients at Carville during the period 1960-1972. The results of the surgery were good in terms of immediate relief of pain, and a neural deficit seldom developed or progressed after the procedure. However, the pain often recurred albeit usually less severe than it had been originally. Although the immediate results of the surgery are, in general, good, one cannot be certain that the long-term results were any better than they would have been without surgery since we have no valid controls. A finding of particular interest is that the procedure has seldom been necessary since 1965 when B 663 and thalidomide were first used at Carville for control of reactions, suggesting that a severe ulnar neuritis is a less likely occurrence in patients receiving these drugs."

17. MEYERS, W. M. & STAPLE, E. M. **Monotony mitigated a mite: or, a superior skin smear slide.** *Int. J. Lepr.,* 1974, v. 42, No. 1, 74-5.

The writers of this letter from Kivuvu Leprosarium, Zaïre, describe the preparation of a slide on which eight skin smears from different parts of the body can be made. A standard microscope slide is coated with paraffin wax and laid on a ruled cardboard pattern. The tip of a scalpel is used to trace through the wax, dividing the greater part of the slide surface into eight equal squares. A portion at the end is left for the identifying name or number. The slide is then placed for 10 minutes in concentrated hydrofluoric acid, washed, and the wax removed by heating and rinsing in xylene. The smears are placed on the unetched side of the slide in a routine sequence. The slides are permanent, and two people can produce up to 200 a day.

F. I. C. Apted

18. DE FARIA, L. L. **Fluorescent staining for *Mycobacterium leprae* in tissue sections. Comparison with Fite-Faraco procedure.** *Int. J. Lepr.,* 1974, v. 42, No. 1, 52-4.

"Leprosy bacilli in tissue sections were stained for fluorescene microscopy. Thirty cases of leprosy with few bacilli were studied. Bacillary positivity was less with this method (33.3%) than with Fite-Faraco procedure (86.6%)."

19. DRUTZ, D. J., O'NEILL, S. M. & LEVY, L. **Viability of blood-borne *Mycobacterium leprae*.** *J. Infect. Dis.,* 1974, v. 130, No. 3, 288-92.

"Noncultivable acid-fast bacilli that circulate in the bloodstream of patients with untreated lepromatous leprosy are viable as judged by their capacity to multiply in the mouse footpad in a manner typical for *Mycobacterium leprae.* The continuous presence of up to 10^5 viable leprosy bacilli/ml of blood both reflects and helps to explain the extreme widespread nature of

infection in patients with lepromatous leprosy. Rifampin 'kills' *Myco. leprae* (i.e., inhibits multiplication in the mouse footpad) much more rapidly than does dapsone, but leprosy bacteremia persists for at least 12-16 weeks with either form of therapy. Circulating *Myco. leprae* are viable for up to six weeks after initiation of dapsone, but for fewer than four weeks after rifampin. Either dead *Myco. leprae* continue to circulate in treated patients, or the footpad technique is not sufficiently sensitive to detect low concentrations of viable *Myco. leprae.*"

20. KRAHENBUHL, J. L., LEVY, L. & REMINGTON, J. S. **Resistance to *Mycobacterium leprae* in mice infected with *Toxoplasma gondii* and *Besnoitia jellisoni*. *Infection & Immunity,*** 1974, v. 10, No. 5, 1068-71.

"Mice chronically infected with the intracellular protozoan *Toxoplasma gondii* or *Besnoitia jellisoni* were resistant to footpad challenge with *Mycobacterium leprae.* Resistance was manifested by lower numbers of recoverable *Myco. leprae* in the footpads of protozoal-infected mice and was enhanced in *Toxoplasma*-infected mice by a booster injection of *Toxoplasma* antigen in the infected footpad. The results suggest a major role for the activated macrophage in the control of *Myco. leprae* infection."

21. KWAPINSKI, J. B. G. & KWAPINSKI, E. H. **Pathobiological relationships between *Mycobacterium leprae* and its primitive host.** *Bull. Wld Hlth Org.*, 1974, v. 50, No. 5, 473-4.

"Newborn snakes were injected with 10^2-10^4 live or heated *Mycobacterium leprae.* Death occurred in 5-6 weeks. On autopsy, the snakes injected with live microorganisms showed pathological changes and numerous acid-fast bacteria were found in some organs. Material was also transferred from an experimentally infected snake to a group of normal newborn snakes, causing their death in three weeks. Extracts in phosphate-buffered saline, prepared from the tissues of infected snakes, were found to react with anti-*Myco. leprae* and anti-*Myco. lepraemurium* rabbit antisera. No immunodiffusion reactions were elicited by extracts from the organs of control snakes."

22. LAHIRI, S. C., SAHA, K., BASU, A. & MITTAL, M. M. **Serum histaminase in leprosy.** *Int. J. Lepr.*, 1974, v. 42, No. 2, 182-5.

"Serum histaminase was estimated in 29 healthy adults and in 36 leprosy patients including 27 lepromatous leprosy and nine tuberculoid leprosy cases. Of the 27 lepromatous leprosy individuals 14 suffered from *erythema nodosum leprosum.* The serum histaminase levels were significantly raised in leprosy patients as compared with normal controls. But there was no significant difference in the enzyme values between patients having lepromatous leprosy without ENL and those with tuberculoid leprosy. However, the value of serum histaminase was found to be further elevated when the lepromatous leprosy patients developed ENL."

23. MUKHERJEE, A. & GHOSH, S. **Study of lepra reaction.** *Int. J. Lepr.*, 1974, v. 42, No. 2, 143-9.

"The present work, undertaken with a view to elucidating the mechanism of lepra reaction, reports significant increase of plasma levels of fibrinogen and a closely related protein, heparin-precipitable-fraction (HPF), in cases of acute lepra reaction. Fibrinolytic activity has also been found to be impaired in them. This may account for the periodic episodes of fibrin deposition in histopathologic material including dermal blood vessels, which were conspicuous

during acute reaction. These patients also revealed variable deficiency in some of the coagulation factors—possibly as a result of 'consumptive coagulopathy'. The relevance of the findings to episodes of lepra reaction has been discussed."

24. BALAKRISHNAN, S., RAMANUJAM, K. & RAMU, G. **Adreno-cortical function tests in lepra reaction.** *Indian J. Med. Res.*, 1974, v. 62, No. 8, 1166-70.

"Adrenocortical function tests were carried out in 27 cases of lepromatous leprosy in the reactive and subsided phases of lepra reaction. The results show a significant lowering of total 17-ketogenic steroids excretion in urine in the patient group particularly in the reactive phase. The response to ACTH administration (carried out in three cases) also indicates a subnormal response. A relative increase in serum potassium level and a lowering of the serum sodium/potassium ratio in the reactive phase is associated with a marked lowering in the urinary excretion of potassium. A mild lowering in blood sugar levels and a flat type of glucose tolerance test are also seen in some patients with lepra reaction. These findings indicate the possible existence of a certain degree of adrenocortical insufficiency in lepra reaction and to a lesser extent in its subsided phase as well. The possible factors responsible for these findings are discussed."

25. OKADA, S., NAKAI, E., NARITA, M., TAKAHASHI, S. & HARADA, N. **Electron microscope study of** *erythema nodosum leprosum. Int. J. Lepr.*, 1974, v. 42, No. 1, 33-7.

"Electron microscopic study by means of the ferritin-conjugated antibody method revealed that the antigenicity of leprosy bacilli is localized in the cytoplasm of leprosy bacilli. In the lesion of ENL, the foamy structure of the lepra cell is ruptured and opens into intercellular spaces and the cell walls of leprosy bacilli are also ruptured. This suggests that antigenic cytoplasmic substance is released from lepra cells. As antibody to the cytoplasm of leprosy bacilli is present in the serum of ENL case, the outflow of cytoplasmic substance of leprosy bacilli results in antigen-antibody reaction which leads to ENL."

[These are interesting results. As two control groups were studied one assumes that the reported findings were special to the ENL group, although little is said about the controls. The illustrations are small, and the magnification stated is perhaps misleading.]

D. S. Ridley

26. BHATT, P. V. & ANTIA, N. H. **Study of viability of** *Myco. leprae* **from multiple tissue biopsies of ten leprosy patients using the mouse foot pad technique.** *Lepr. India,* 1974, v. 46, No. 2, 73-82.

From two patients with lepromatous leprosy, four with borderline-lepromatous, and four with borderline-tuberculoid leprosy, biopsy specimens were taken of skin, lymph node, dartos, nasal mucosa, nerve, and striated muscle, homogenized and injected into footpads of mice. Six patients had received treatment albeit "irregular" in three and of short duration in two. From the four patients with borderline-tuberculoid leprosy, only the nerves contained *Mycobacterium leprae*. From the other patients the nerves contained the largest number of bacilli per g, and also in these tissues the morphological index was higher than in the other tissues [although no figures of the latter index are given and these might have explained the statements that the growth rate of bacilli from tissues other than nerves was slower].

C. S. Goodwin

27. FILDES, C. **Organized nerve tissue cultures infected with** *Mycobacterium leprae* **and** *Mycobacterium lepraemurium. Int. J. Lepr.*, 1974, v. 42, No. 2, 154-61.

"Organotypic cultures of dorsal root ganglia and of whole cross sections (muscle somite, cord and ganglia) were prepared from rat and mouse fetal tissue. Duplicate cultures were inoculated with *Myco. leprae* and *Myco. lepraemurium* respectively and compared with controls (uninfected cultures) over an incubation period of 50 days. There was no evidence of a cytotoxic reaction to the bacilli. Following fixation and staining, the cultures inoculated with *Myco. leprae* were found to contain large numbers of bacilli at the end of the 50-day incubation period, whereas those inoculated with *Myco. lepraemurium* were comparatively free of bacilli. With the electron microscope, cultures inoculated with *Myco. leprae* can be further distinguished from those inoculated with *Myco. lepraemurium* by the formation of large vacuolated inclusion bodies and by the presence of extremely large myeliniform figures, contained mainly within macrophages and fibroblasts.

"Rat and mouse dorsal root ganglia were equally susceptible to infection with *Myco. leprae.* No infection of cord tissues was observed. It is suggested that this exposure period (of less than two months) may not be long enough to encompass major involvement of Schwann and satellite cells."

28. LEVY, L., MOON, N., MURRAY, L. P., O'NEILL, S. M., GUSTAFSON, L. E. & EVANS, M. J. **Studies of the mouse footpad technic for cultivation of** *Mycobacterium leprae.* **I. Fate of inoculated organisms.** *Int. J. Lepr.*, 1974, v. 42, No. 2, 165-73.

"The possibility of loss from the mouse footpad of a large fraction of an inoculum of *Myco. leprae* was suggested by a preliminary experiment, and a systematic investigation of this problem was undertaken. A series of experiments with various inocula, including freshly harvested *Myco. leprae, Myco. leprae* stored at 4°C, *Myco. marinum,* and suspensions of ^{99m}Tc-sulfur colloid all yielded much the same result: 60% to 90% of the inoculum could not be recovered by a harvest performed soon after footpad inoculation. The recovery of organisms added to footpad tissue harvested from uninoculated mice was nearly complete, excluding the possibility of an inherent deficiency of the harvesting procedure. Recovery of the inoculum was improved somewhat when a more extensive harvest was done, but much of the inoculum remained unaccounted for. Inoculum was lost even when dead mice were inoculated, and when anesthetized mice were inoculated to minimize the possibility of leakage. When radioactive colloidal particles of about the same size as *Myco. leprae* were inoculated, traces were found in the blood, liver, spleen and inguinal lymph nodes, but the quantities of the radioactive material in these organs were smaller than expected if that fraction of the inoculum lost from the footpad were distributed uniformity among all of the tissues of the mouse.

"Loss of a large fraction of inoculated *Myco. leprae* from the mouse footpad occurs regularly, does not represent an artifact, and is not the result of leakage of the inoculum. Loss occurs probably by way of the circulation. The organisms lost from the footpad do not appear to be uniformly distributed in the mouse, suggesting that they may be taken up preferentially from the blood by some organ such as the bone marrow."

29. LEW, J., YANG, Y. T. & PYUN, W. S. **Experimental infection of the Korean chipmunk (*Tamias sibiricus asiaticus,* Gmelin) with** *Myco. leprae. Int. J. Lepr.,* 1974, v. 42, No. 2, 193-202.

"1. *Myco. leprae,* obtained from lepromatous nodules either by conventional grinding or trypsin purification methods, multiplied in both footpads and ears of the Korean chipmunks through the first and the second passage experiments. Growth of *Myco. leprae* in these inoculated tissues became evident after a lag phase of approximately seven months post-inoculation.

"2. Characteristic leprotic changes were observed in footpads of the chipmunks inoculated with trypsin-purified *Myco. leprae* 13 and 16 months previously, and these changes included extensive leproma formation, the presence of massive numbers of acid-fast bacilli in the foam cells and the involvement of dermal nerve fibers by acid-fast bacilli.

"3. Among the chipmunks inoculated with trypsin-purified *Myco.leprae* for the preparation of the chipmunk lepromin antigen, apparent swelling of the inoculated tissues was observed in a considerable number of the chipmunks at ten months after inoculation. Two such swollen footpads contained 2.0×10^{10} acid-fast bacilli each.

"4. The results of skin tests in a series of leprosy patients with the chipmunk lepromin antigen, prepared with acid-fast bacilli harvested from swollen infected footpads, were identical with those of standard lepromin antigen prepared from biopsied lepromatous nodules."

30. WLD HLTH STATIST. REP., 1974, v. 27, No. 12, 750-52. **Leprosy.** [In English and French.]

Monthly and annual figures for the numbers of cases of leprosy reported to WHO in 1973 and 1974 are given for more than 60 countries. Those for 1974, and in some instances for 1973, are incomplete. In Africa the highest figures for 1973 were reported by Chad (1298 cases), Mali (2798), and Senegal (1705). In Central America, Cuba reported 266 cases and Surinam 151. In Asia, the highest 1973 totals were in Sri Lanka (749), Philippines (615), and West Malaysia (318). In Europe, the Netherlands reported 50 cases, Portugal 35, Spain 26, and France 14. Other European countries reported a few cases; there is no report from the U.K. The United States reported 135 cases in 1973.

F. I. C. Apted

31. SEAL, S. C. & GHOSE-HAZRA, A. **Clinico-epidemiological study of leprosy in Calcutta. Follow-up work at the homes of the patients, and suggestions for control measures.** *J. Indian Med. Ass.*, 1973, v. 61, No. 9, 375-82.

Many of the problems of leprosy control in the sprawling, overcrowded city of Calcutta are brought out in this paper. The situation is probably worse now than when the reported figures were collected (that is, before 1972). Each year (from 1961 to 1966), 4093 cases of leprosy (on average) were diagnosed at the leprosy clinic of the School of Tropical Medicine. Of these, 23.7% had lepromatous leprosy; about 60% had, for two or three years, indications that they suspected were due to leprosy, before presenting themselves at the clinic. In this series, adults were no less susceptible to infection than children. Over half the patients had apparently contracted the disease while resident in Calcutta itself.

Very few of the patients (only 8.3%) admitted any history of contact, a finding that suggests that, in an area of such prevalence, opportunities for infective contacts must be of very frequent occurrence.

The authors discuss the epidemiological implications of the enquiry, with particular reference to the unknown or unidentified sources of infection, the age of first infection of the majority of the population (even those in close household or conjugal contact with index cases), and the ubiquitous nature of the endemic in all social groups. Leprosy is becomming an urban disease in India, with changing epidemiological features. While a welcome decrease in social stigma is noticeable, community attitudes to the disease itself and to its victims still play an important—perhaps decisive—role in the success of the leprosy campaign. The authors make several unexceptionable suggestions for the control of leprosy in the urban context of present-day Calcutta.

S. G. Browne

32. KAPOOR, K. K. & GUPTA, S. C. **Serum cholesterol and alkaline phosphatase in different types of leprosy.** *Lepr. India,* 1974, v. 46, No. 3, 152-6.

"Serum cholesterol was found to be significantly decreased in all types of leprosy. No correlation between the decreased levels of serum cholesterol and severity of the disease was observed. Serum alkaline phosphatase was found to be within normal limits in different types of leprosy. The values in patients with tuberculoid type of leprosy were similar to those among normal healthy control subjects. In all other types of leprosy the values were found to be on the higher side of normal range. This slight increase from the mean normal value was statistically significant in sera from patients dimorphous, lepromatous and lepra-reaction."

33. BHUTANI, L. K., BEDI, T. R., MALHOTRA, Y. K., KANDHARI, K. C. & DEO, M. G. **Histoid leprosy in North India.** *Int. J. Lepr.*, 1974, v. 42, No. 2, 174-81.

The authors describe the clinical, bacteriological and histological findings in 20 patients suffering from histoid leprosy at the All India Institute of Medical Sciences, New Delhi. In seven patients histoid lesions were the first signs of leprosy noted; the remaining 13 developed them five months to 14 years after their disease began. Some unusual histological features were observed.

[Cases 8 and 18 are labelled borderline, but the presence of histoid nodules indicates that they have downgraded to lepromatous and are in the sub-polar lepromatous group.]

W. H. Jopling

34. DHARMENDRA. **Infectivity of "open" cases of leprosy under treatment.** *Lepr. India,* 1974, v. 46, No. 3, 188-91.

The author reviews the "highly controversial" subject of the non-viability of non-solidly staining leprosy bacilli and concludes:—

". . . that there is no conclusive evidence to justify any change in our existing criteria of non-infectivity of 'open' cases under treatment. On the other hand, there are cogent reasons against affecting a change in the criteria. In the author's opinion it would be wise to stick to old criteria based on bacteriological negativity (B.I. Zero) of multiple skin smears, and maintained at examinationns repeated over three consecutive months. After that the patient should be examined every six months to ensure that he continues to be negative. The period of this six monthly check up will vary according to the type and past severity of the disease, and on the period for which the patient had remained positive prior to becoming negative."

35. NAVALKAR, R. G., PATEL, P. J., DALVI, R. R. & LEVY, L. **Immune response to *Mycobacterium leprae:* plaque-forming cells in mice.** *Infection & Immunity,* 1974, v. 10, No. 6, 1302-6.

"Intravenous immunization with a cell extract of *Mycobacterium leprae* produced a primary immune response of considerable magnitude, followed by an equally large response after secondary stimulation, as measured by assay of plaque-forming cells (PFC). Infection with *Myco. leprae* or immunization with cell extract by the footpad route produced a lower level of response than that seen in the intravenous group. Identical patterns of response, although not of the same magnitude, were observed after both primary and secondary challenges in the two footpad groups, one infected with viable *Myco. leprae* and the other immunized with *Myco. leprae* cell extract. The secondary response after a booster dose to all these groups appeared to be an enhanced immunoglobulin M response. Control studies confirmed that the immune response was a direct result of the host-parasite interaction and that the PFC observed resulted from stimulation of antibody-forming cells by antigens of *Myco. leprae.* The similarity in time

of appearance of peak PFC levels in the two footpad groups may be attributed to the live challenge passing through a latent phase. Alternatively, the challenge is known to contain a large proportion of nonviable cells, and it may also contain soluble *Myco. leprae* antigens. Studies of the cross-reactivity of the antigens have extended previous observations on antigens shared between *Myco. leprae* and other mycobacterial species. Use of the two antigen-containing fractions of the *Myco. leprae* cell extract has suggested that one of the fractions contains some shared antigens, whereas the other has an antigen specific to *Myco. leprae.*"

36. CLOSS, O. & HAUGEN, O. A. **Experimental murine leprosy. 3. Early local reaction to *Mycobacterium lepraemurium* in C3H and C57/BL mice.** *Acta Path. Microbiol. Scand. Sect. A,* 1975, v. 83, No. 1, 51-8. **4. The gross appearance and microscopic features of the local infiltrate after subcutaneous inoculation of C3H and C57/BL mice with *Mycobacterium lepraemurium.*** *Ibid.,* 59-68.

"*Myco. lepraemurium* was injected subcutaneously into two inbred strains of mice, C3H and C57/BL, in order to study the local reaction at various time intervals. Within six hours an acute inflammatory reaction developed at the site of injection. In the course of the following days it was replaced by a mononuclear infiltrate. The influx of mononuclear cells appeared to be somewhat greater in C57/BL than in C3H mice. Apart from this, little difference was observed between the two strains until at four weeks when a vigorous granulomatous reaction developed in the C57/BL strain. This reaction apparently arrested further local spread of the infection. The histological appearance of the infiltrate indicated that a delayed hypersensitivity reaction was taking place. No sign of such reaction was observed in the C3H strain.

"Mice of the inbred strains C57/BL and C3H were inoculated subcutaneously on the thorax with *Myco. lepraemurium.* In C57/BL mice a firm, raised, sharply defined nodular infiltrate developed four weeks afterwards, while in the C3H strain the infection produced a soft, flattened infiltrate with ill-defined margins, which did not become palpable until 10 weeks after inoculation. A limited spread of the infection occurred early in both strains, but apparently multiplication of the microorganisms was very restricted in C57/BL mice; progressive, disseminated growth of the bacilli was observed in the C3H strain only. In C57/BL mice the granulomatous reactions, developing four weeks after inoculation and leading to abscess formation, ulceration and scar formation, apparently inhibited both local multiplication and further spread of the bacilli. In C3H mice no host reaction was detected and the bacilli appeared to grow unrestrictedly. In some C57/BL animals, decrease in host resistance occurred during the infection, causing reactivation of the local lesion and an apparently rapid proliferation of bacilli. Observations regarding the lesions in superinfected animals indicated that a systemic immune reaction develops in the C57/BL strain about four weeks after inoculation, whereas this does not occur in the C3H strain."

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3 year contract in Malawi

Leprosy work in Malawi is entering a new phase with the expansion of domicilary treatment to areas outside the original LEPRA project. A framework has been set up, which, within the next few years, will ensure coverage of the whole country.

The Ministry of Health in Malawi is looking for a Dermatologist aged 25–50, with a medical degree obtained in the U.K. and post-graduate experience in dermatology and leprosy control.

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