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Editorial

PROBLEMS AND OPPORTUNITIES IN THE THERAPY OF LEPROSY

We now have a useful range of antileprosy drugs from which to choose, and the two chief problems confronting the clinician are the side effects of these drugs and the emergence of drug resistant strains of *Mycobacterium leprae.*

Side effects of antileprosy drugs

Here we are concerned not only with direct effects of the drug in use but also with indirect effects in the form of reactional states (lepra reactions). As regards direct side effects, and taking *dapsone* first, the chief advantage of this drug (apart from its low cost) is its relative lack of toxicity. Haemolytic anaemia is the most important side effect, and interest centres on dapsone's capacity to induce haemolysis in persons who are deficient in glucose-6-phosphate dehydrogenase (G6PD). On the face of it one would expect haemolytic anaemia to be a troublesome complication in the management of leprosy, but this is not so for it is rarely encountered even in populations with the highest incidence of enzyme deficiency—Africans and those with African ancestry. One explanation lies in the fact that different types of G6PD deficiency predominate in different ethnic groups; for example, the African type is characterized by a mild enzyme deficiency, the Mediterranean type by severe deficiency, and variations are present in East and South-East Asia (*W.H.O. Chronicle*, 1974). Another explanation is that the dosage of dapsone generally employed today (700 mg/week or less) is below the level likely to induce haemolysis of clinical significance. *Clofazimine* (Lamprene; B663) is a safe drug to use but has the disadvantage of causing unsightly skin pigmentation, especially in persons with light skins, and it is doubtful if this side effect will ever be overcome because of the nature of the dye and its tendency to be selectively deposited in leprosy lesions by macrophages. I have a patient who stopped clofazimine therapy 5 years ago but is still embarrassed by slate coloured markings on his face. Serious side effects of *rifampicin*, of which liver damage is the most important, have been recorded in the treatment of tuberculosis when this antibiotic has been given in interrupted dosage such as twice a week, but can be much reduced by regular daily dosage, so much so that it can now be said that "liver toxicity with rifampicin does not seem to be a major problem" (Leading Article, 1973). *Thiambutosine* (Ciba, 1906) is unique in being devoid of direct side effects.

Turning to the indirect side effects of antileprosy drugs we come to the subject of reactional states—the leprologist's bugbear. Although lepra reactions were known before the introduction of effective therapy, the incidence has increased with the advent of the sulphone group of drugs in the 1940's, and it has since become apparent that other effective antileprosy drugs also have a reaction-

producing capacity. Waters and Helmy, in their paper in the present Number of this Journal, demonstrate that ENL reaction in lepromatous leprosy (type 2 reaction) is not directly due to dapsone but is consequent upon the killing of leprosy bacilli, and the next stage in research on this subject will be to explain the mechanism whereby dead bacilli trigger a rapid change in cell-mediated immunity (CMI) in borderline leprosy (type 1 reaction) and an immune complex syndrome in lepromatous leprosy. Are lepra reactions dosage dependent? In other words, is high dosage of dapsone more likely than low dosage to precipitate them? This is a question of great concern to clinicians, for it is natural for them to presume that larger dosage increases the rate of destruction of leprosy bacilli and thereby increases the incidence of reaction. In fact, many clinicians over the past two or three decades have gained a strong impression that the incidence and severity of lepra reactions are dosage dependent. However, a preliminary trial in lepromatous patients at Sungei Buloh, Malaysia, has failed to confirm this impression (Pearson and Helmy, 1973), and further controlled trials on this important subject are indicated.

Two drugs require special mention on this question. The first is *clofazimine* (Lamprene; B663), a drug which combines an antileprosy effect as good as that of dapsone with an anti-inflammatory action capable of controlling some manifestations of lepra reaction, and the point of special importance is dosage. The odd situation is that one capsule of 100 mg twice a *week*, while being an effective therapeutic dose, is useless in controlling lepra reaction (and, in fact, can precipitate it), whereas larger dosage in the region of one capsule two to four times a *day* can control it. The other drug is *rifampicin*. There were fears, when it was introduced into the treatment of leprosy, that its rapid bactericidal effect against *Myco. leprae* might result in a high incidence of lepra reaction, but this has not been borne out by subsequent experience. Although this may be explained by the rate of release of intracellular antigens of *Myco. leprae*, a more likely explanation is immunosuppression as rifampicin has been shown to have an immunosuppressive effect, not only in man and animals, but also *in vitro* as judged by experiments on human lymphocytes which have demonstrated its inhibiting action on (1) blastic stimulation by phytohaemagglutinin, and (2) the secretion of migration-inhibiting factor (Serrou, 1974).

Resistance to antileprosy drugs

Sulphones. The incidence of sulphone resistance in lepromatous leprosy is undoubtedly increasing, and attention focuses on two aspects of sulphone therapy: low dosage and irregularity of treatment. On the first point a decision has to be made on what constitutes low dosage, and so far this has not been made. Most leprologists appear to accept dosages in the region of 100 mg/week as low, but this I would not accept. In my opinion dosages of 5 mg/day (35 mg/week) or less should be considered low, and this is an important question requiring attention. The paper by Gelber *et al.* in the present Number of this Journal supports the contention that low dosage is a factor in causing sulphone resistance, but on the other hand there has been no report of relapse of lepromatous leprosy in patients receiving an injection of DADDS (Hansolar; acedapsone) regularly every 75 to 77 days, a dosage which liberates only 2.4 mg of dapsone into the tissues daily. The fact that there have been relapses of lepromatous leprosy a year or more after stopping DADDS injections has nothing to do with dosage as relapses can occur in patients who stop taking 100 mg daily. In support of the

view that irregularity of treatment encourages sulphone resistance we have the report of Jacobson and Trautman (1971) who recorded a high incidence in lepromatous patients who had been irregular on treatment; there was no question of any of these patients taking low dosage of sulphone. In my own experience I have not encountered sulphone resistance in lepromatous patients taking 5 mg/day *regularly* and from the beginning of treatment, but have a number of patients who developed resistance on 100 mg/day; they all had been irregular on treatment and had suffered one or more relapses after stopping treatment against medical advice. This aspect of the problem requires more research, as does the proposition of combating drug resistance by giving dapsone in combination with another antileprosy drug. Although this would seem the most logical approach it is doubtful if combined therapy will prove practicable in developing countries because of expense.

Other antileprosy drugs. It is generally accepted that drug resistance in lepromatous leprosy develops after two to three years of treatment with thiambutosine (Ciba, 1906) and thiacetazone (TB1), but so far there have been no reports of resistance to clofazimine or to rifampicin.

Immunotherapy

On the basis that the poor prognosis in lepromatous leprosy is due to depression of cell-mediated immunity (CMI) against *Myco. leprae*, whereas the good outlook for cure in tuberculoid leprosy is due to the possession of CMI, research is now in progress on the possibility of transferring cellular immunity to lepromatous patients by injecting lymphocytes or extracts from leucocytes (transfer factor) derived from tuberculoid patients or from healthy donors hypersensitive to lepromin. The first attempt at this line of treatment was reported by Bullock *et al.* (1972) and a number of centres are now developing it, but it is still in the experimental stage. All that can be said at the present time is that it holds out great promise for the lepromatous patient and marks an important stage in the better understanding of leprosy and its management.

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Ten Years of Dapsone in Lepromatous Leprosy: Clinical, Bacteriological and Histological Assessment and the Finding of Viable Leprosy Bacilli*

M. F. R. WATERS

Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, Malaysia

R. J. W. REES†

National Institute for Medical Research, Mill Hill, London, NW7 1AA

A. C. McDOUGALL

A. G. M. WEDDELL

Department of Human Anatomy, Oxford University, Oxford, OX1 3QX

Twelve lepromatous patients who had completed 10 to 12.5 years' continuous chemotherapy, principally or entirely with dapsone, were assessed clinically, bacteriologically and histologically. In all 12 the disease showed full clinical response to therapy, although three patients remained smear positive, and two of these still suffered from mild *erythema nodosum leprosum*. However, by mouse footpad inoculation it was shown that seven of the 12 patients still harboured viable *Myco. leprae*. Thus bacterial multiplication was obtained in mice inoculated with 10 of 37 tissue suspensions prepared from extensor skin (4), striated muscle (3), peripheral nerve (2) and smooth muscle (1), although the numbers of positive footpads in each group of mice were small, in keeping with the minute numbers of leprosy bacilli, of variable viability, inoculated. No bacterial enhancement was obtained in thymectomised-irradiated mice, and three of six strains died out on passage; these findings recalling the difficulties encountered by McCune *et al.* in culturing *Mycobacterium tuberculosis in vitro* from tuberculous mice subjected to effective chemotherapy. Three of these strains of *Mycobacterium leprae* (two from skin and one from nerve) from separate patients, were shown to be fully sensitive to dapsone. The importance of these findings is discussed, especially with regard to clinical relapse of leprosy after premature stopping of treatment and to the total duration of dapsone therapy required in lepromatous leprosy.

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† Requests for reprints should be sent to R. J. W. Rees.

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Introduction

There are two major paradoxes in the chemotherapy of lepromatous leprosy. First, whereas the initial response to sulphone treatment is encouraging, long-term clinical results may be very unsatisfactory (Jacobson and Trautman, 1971). Second, although the Morphological Index (MI) rapidly falls after commencing dapsone (DDS) therapy, to reach baseline after about 4.5 months (Waters, Rees and Sutherland, 1967), and although after approximately three months' treatment, leprosy bacilli obtained from skin biopsies may no longer infect mouse footpads (Shepard, Levy and Fasal, 1968) yet bacterial reactivation with clinical relapse may occur after many years of treatment.

In the experience gained over the last 10 years at Sungei Buloh Leprosarium (Pearson and Waters, unpublished data), patients who relapse (clinically and histologically) while still receiving dapsone have developed sulphone resistance, whereas those who relapse through failure to continue on therapy in general are still harbouring sulphone-sensitive strains of *Mycobacterium leprae*. It may be argued that some relapses in the latter group are due to re-infection with *Myco. leprae*. But in the majority of cases the weight of probability, both on clinical and on general bacteriological grounds must be that small numbers of viable leprosy bacilli persist in the patient for long periods after the start of successful chemotherapy (see Committee of Experimental Chemotherapy, 1973). We have suggested (Waters and Rees, 1962; Waters, 1967; Ellard, 1974) that these viable bacilli may be present in special sites, such as Schwann cells and smooth and striated muscle fibres.

To investigate this hypothesis, we have examined fully, both clinically and experimentally, 12 fully documented lepromatous patients who had completed 10 to 12.5 years of continuous anti-leprosy treatment. Here we present a preliminary report of our findings.

Materials and Methods

The 12 patients were unselected volunteers from among those still available from a group of some 80 previously untreated lepromatous subjects investigated by one of us (MFRW) during the years 1959-1962 for admission to controlled clinical trials. Full clinical, bacteriological, histological and treatment records were available. Ten were Chinese, two were Southern Indian, all were males. Their ages on first admission ranged from 16 to 66 (average 38) years. Both clinically and histologically, all had been classified LL or LI on the modified Ridley-Jopling spectrum (Ridley and Jopling, 1966; Ridley and Waters, 1969), and all had suffered from moderately or markedly severe leprosy ("L2" or "L3", as defined by Quagliato, Bechelli and Marques, 1970). Their admission smears had given average Bacterial Index (BI) of 4.5 with a range of 3.7 to 5.2 on Ridley's logarithmic scale (Ridley, 1958); the pretreatment MI was known in 11 patients and averaged 44 (range 20 to 74). Their lepromin (Dharmendra) skin test had been negative.

All had received initially one year of dapsone by intramuscular injection, 200 mg twice weekly for the first six weeks and then 300 mg twice weekly. Thereafter the dosage was more variable, between 50 and 400 mg twice weekly, and some patients had been changed to oral dapsone. During their second and fourth year of treatment respectively, two patients with severe *erythema*

nodosum leprosum (ENL) (nos. 4 and 2) had been switched to thiambutosine in the dosage 1 g b.d. for 17 months, before recommencing dapsone. Two other patients (nos. 10 and 11) had received clofazimine (B663) for 12 and 42 months respectively, the former for persisting neuritis and the latter for severe ENL; dapsone was given simultaneously with the clofazimine for six months (no. 10) and for 28 months (no. 11). A fifth (no. 3) had additionally received streptomycin for two years for pulmonary tuberculosis. Nine patients had suffered from ENL, but had been kept throughout on full and regular treatment. Only one patient (no. 1) was not still taking regular treatment at the time of the re-examination—he had stopped against advice eight months earlier, after more than 12 years' continuous treatment. Eight were still living in, or close to the leprosarium, while four outpatients, although living further away, attended regularly for their supplies of dapsone.

The "ten year" assessment was carried out, ten years after commencing treatment in nine patients, eleven years in two and 13 years in one (average 10.5 years, range 9 years 11 months to 13 years 1 month). The patients were fully examined clinically by the same observer as a decade earlier. Photographs were taken and compared with the pretreatment photographs. Smears were taken from both ear lobes and from at least four representative skin sites, the pretreatment sites being chosen unless alternative sites were indicated. Urine specimens were collected for routine examination and for estimation of dapsone concentration. Lepromin (Wade-Mitsuda) and tuberculin (1 TU of RT23) skin tests were performed in eight patients. Biopsies were obtained of extensor skin, triceps muscle, superficial radial nerve, and in five cases also of scrotum for dartos (smooth muscle). Aliquots of skin were fixed in Ridley's fixative, and of all sites in Richardson's solution, for histological examination. Other aliquots were flown on wet ice to the National Institute for Medical Research, London, where they were extracted for acid-fast bacilli (AFB), and the resulting suspensions were inoculated into the footpads of groups of six normal and/or thymectomised irradiated (T900R) mice, whether or not AFB could be detected (Rees, 1971). The mice were harvested individually after 12 months, counted, and suspensions found positive for AFB were passaged.

Additional extensor skin, nerve (superficial radial or sural) and dartos biopsies were taken from nine of the 12 patients from one year to three years eight months after the "10-year" examination (i.e. from 11 years 1 month to 14 years 6 months, average 12 years 9 months after first commencing treatment). During this time all 12 patients were still on regular dapsone treatment, patient no. 1 having been restarted from the date of the principal examination.

Results

CLINICAL

The general appearance of all 12 patients was good, compatible with quiescent, fully treated lepromatous leprosy (Fig. 1). Nine were smear negative, three (patients nos. 2, 7 and 11) were still positive at one or two only of the six sites, where individual BIs were 1+ to 3+; all bacilli seen were fragmented (MIs were 0). Two of the three smear-positive patients had evidence of mild ENL (nos. 7 and 11).

Over the decade, anaesthesia had increased slightly in six patients, although

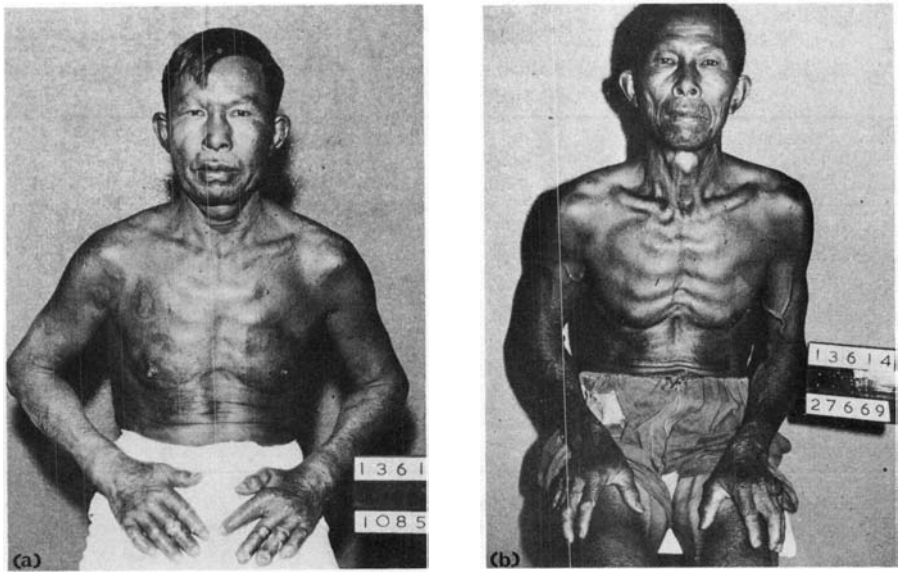

Fig. 1 Representative picture of lepromatous patient (No. 4) before start of treatment (a) and after 10 years of continuous treatment (b).

nerves in general had become smaller. However, two LI patients showed further unilateral enlargement of ulnar nerves originally related to initial borderline lesions on the forearm; both patients (nos. 6 and 10) had suffered from neuritis and had eventually received "nerve slits" after increased muscle wasting had developed. Eight others showed slight increase in muscle weakness and/or wasting (most commonly increased weakness of toe abduction), compared with pretreatment; two showed no significant change. Two patients (nos. 4 and 10) had superficial anaesthetic plantar ulcers at the time of review and a third (no. 3) had developed slight atrophy of some anaesthetic digits over the decade.

None of the 12 patients had undergone a reversal reaction, and the eight who were retested remained lepromin negative.

HISTOPATHOLOGY

Skin. In respect of infiltrating cells, all 12 specimens were abnormal. They showed streaks or clumps of old foamy lepromatous infiltration mainly around dermal appendages, especially sweat glands and arrector pili muscle, but also following neuro-vascular pathways. The cell type was predominantly foamy histiocyte, with occasional lymphocytes and a few plasma cells. The dermal nerves were present in all but two instances and showed changes varying from slight fibrosis to total collagenisation of the endoneurium with multilayering of the perineurium. Granular AFB, or bacterial debris were found in four patients.

Striated muscle (triceps). This was available from 11 patients, and only two showed any abnormality, consisting of a slight histiocytic and lymphocytic

TABLE 1

Details of Myco. leprae *isolates obtained in footpads of mice inoculated with various tissue suspensions from the 12 patients*

Myco. leprae isolates	Origin of tissue suspensions				
	Skin	Muscle	Nerve	Dartos	Total
No. of isolates attempted	13[a]	12	7	5	37
No. of isolates successful	4	3	2	1	10
No. of passages attempted	3	2	1	0	6
No. of passages successful[b]	2	0	1	0	3

[a] Included two skin biopsies from patient no. five.
[b] Skin biopsies from patients nos. 3 and 5; nerve biopsy from patient no. 11.

TABLE 2

Data showing dapsone sensitivity in mice of the three passaged strains of Myco. leprae

Source of *Myco. leprae*	Proportion of mouse footpads showing multiplication			
Patient no. and tissue	Normal mice		T/900R mice[a]	
	UTC[b]	DDS[c]	UTC	DDS
3, skin	–	–	7/12[d]	0/12
5, skin	8/12	0/12	8/8	–
11, nerve	–	–	2/10	0/10

[a] T/900R = mice subjected to adolescent thymectomy followed by whole body irradiation.
[b] UTC = untreated control mice.
[c] DDS = mice fed with 0.0001% dapsone in their diet.
[d] Yields of bacilli were not enhanced in any of the groups of T/900R mice.

infiltrate between fibres. In both patients a single AFB was found in this infiltrate after intensive searching.

Nerve. The superficial radial was available from all 12 patients, and the sural was examined from four. One biopsy was completely normal, and one showed only slight perineurial thickening, barely beyond the limits of normality, but all others were abnormal, often markedly so. Changes varied from slight proliferation of perineurial cells through varying degrees of cellular infiltration to gross disorganization of epi-, peri-, and endoneurial elements. In over half the specimens, foamy histiocytes, destroyed Schwann cells and collagen formation

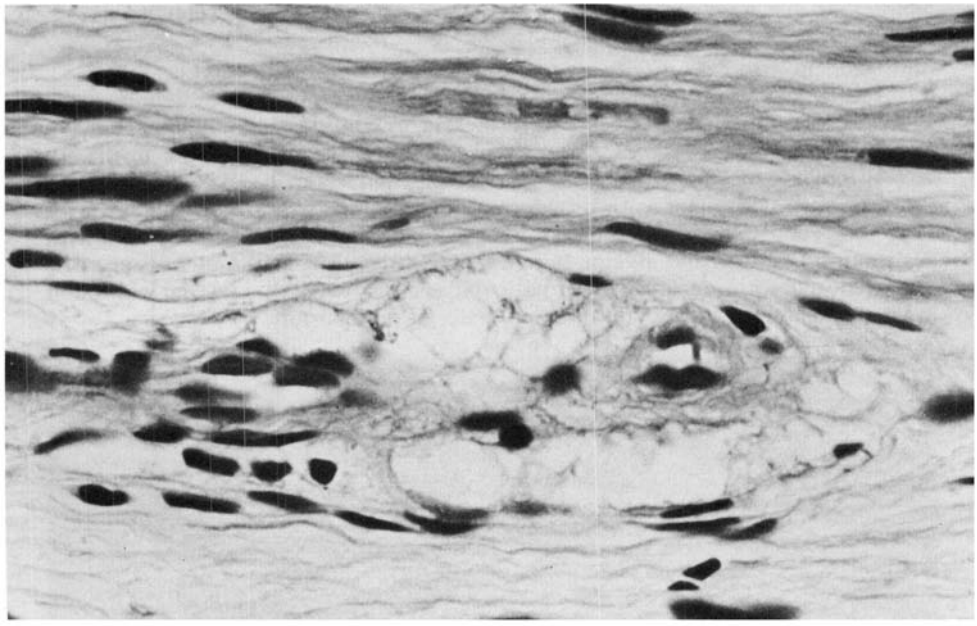

Fig.2.In the substance of endoneurium, foamy histiocytes and occasional lymphocytes have completely replaced Schwann cell, axonal and myelin elements. TRIFF stain. X 3750.

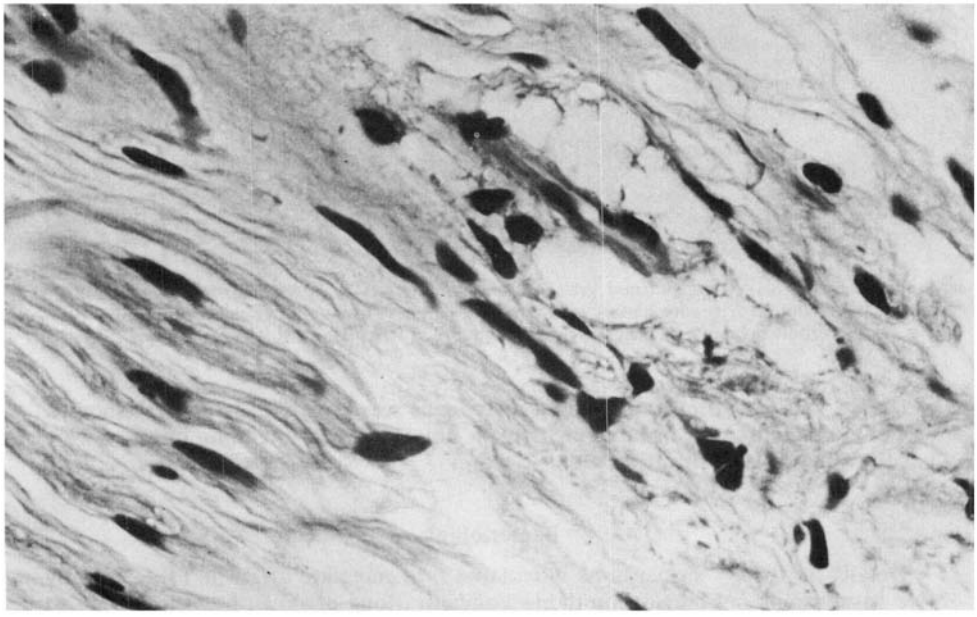

Fig.3.Close to normal neural elements in the endoneurial area (left), the perineurium (right) shows extensive destruction and replacement by foamy histiocytic infiltration. TRIFF stain. X 3750.

were seen in association with axonal and myelin abnormalities (Figs 2 and 3). Infiltrating cells were mainly foamy histiocytes but in several cases lymphocytes, and less commonly plasma cells, were present in considerable numbers (Fig. 4). Epineurial blood vessels were often hypertrophied, especially in the media. In several biopsies it appeared that the entire nerve substance had been replaced by fibrous tissue, consonant with total loss of functioning axons. In one patient with continuous and formerly severe ENL, marked endoneurial changes were seen with destruction of axons and myelin, lymphocytic infiltration, and numerous necrotic cells with pyknotic nuclei. In four patients, acid-fast bacillary material was found in the cytoplasm of histiocytes in either endo- or perineurium.

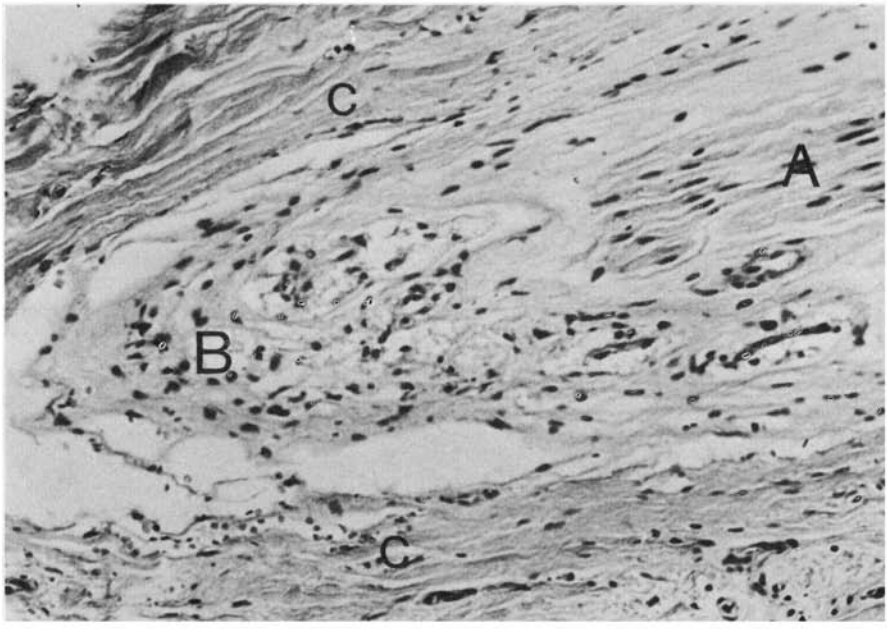

Fig.4. Adjacent to surviving normal axons and Schwann cells at A, the endoneurium (B) shows infiltration with foamy histiocytes, lymphocytes and a few plasma cells. The perineurium at C is multilayered and extensively collagenised. TRIFF stain. X 936.

Dartos (with scrotal skin). Eight specimens were examined. Several showed atrophy and reduction in number of plain muscle fibres, but in no instance were bacilli found or an infiltration seen.

Bacteriology

Details of the 37 suspensions inoculated into mice are given in Table 1. Only five suspensions contained countable concentrations of AFB, but these were so low that mouse inocula consisted of only 1 to 8 x 10^2 bacilli. For the remaining 32 suspensions in which no AFB could be detected, the numbers of bacilli inoculated were presumably even smaller.

Only two of the five "positive" suspensions multiplied in mice, including one skin specimen from patient no. 5, where seven of 12 footpads showed multiplication. But the other "positive" and the eight "negative" suspensions which also multiplied in footpads, gave very few takes (1 to 3) in each group of animals. Yields also tended to be low, from 5×10^4 to 1.2×10^6 bacilli, and no enhancement was obtained in T900R mice. Passage was attempted of 6 strains yielding positive footpads; three were successful (skin suspensions of patients nos. 3 and 4 and nerve of no. 11) in normal and/or T900R mice, and the bacilli proved fully sensitive to dapsone (0.0001% dapsone in the mouse diet)—see Table 2. Two strains, however, have failed to passage and the third died out on second passage.

Discussion

Even today, 33 years after the introduction of sulphone therapy, there is no accurate data to guide the physician on the duration of dapsone treatment required to cure lepromatous leprosy. Reactivation of the disease after premature stopping of treatment remains a major hazard, especially in view of the high percentage of patients "lost to control" or "out of control" in many national leprosy control schemes (Bechelli, 1971). Some earlier accounts of relapse may well have included borderline-lepromatous (BL) as well as lepromatous (LI and LL) disease, thereby presenting an unduly optimistic picture. The majority of more recent publications have confined themselves to recording the reappearance of leprosy bacilli in the smears of negative patients, without reference to the BI or the MI, nor to histological or clinical signs of relapse, and have failed to allow for sampling error associated with the patchy distribution of fragmented (dead) leprosy bacilli in the skin of much-treated patients. A notable exception is Price (1959), who reported clinical and histological as well as bacteriological relapse in six patients (an incidence of 25%) who had ceased chemotherapy on achieving smear negativity 30 to 66 months (average 44 months) after commencing treatment; on average, clinical relapse developed 27 months after stopping chemotherapy. Noordeen (1971) has recently listed the data required to evaluate the precise significance of relapses occurring in any series of patients. He concluded that (bacteriological) relapse is a common feature of lepromatous leprosy, especially among smear negative patients who discontinue treatment.

There is clearly a great need for more information on the incidence of relapses after various durations of anti-leprosy treatment, and even more urgently for scientific data on their possible mechanisms. This is particularly so, because of the current confusion and misconception concerning the effect of chemotherapy on *Myco. leprae.* We have repeatedly shown that leprosy bacilli respond rapidly to standard anti-leprosy treatment so that the MI reaches baseline in approximately 4.5 months, or with rifampicin after only four to six weeks. Shepard, Levy and Fasal (1968, 1972) and ourselves (Rees, Pearson and Waters, 1970) have likewise shown that it is difficult to infect mice with *Myco. leprae* obtained from the skin of patients treated for three months or more with standard dapsone therapy, or a few days or more with rifampicin. But partly because of the frequent occurrence of relapses, Bechelli and Guinto (1970) and Dharmendra (1973) have cast doubts on the value of the MI and of the mouse footpad infection. In fact, apart from the development of dapsone resistance, there are two simple explanations for relapses. As effective immunity is never normally developed in lepromatous leprosy, re-infection is always theoretically possible once chemotherapy ceases. Alterna-

tively, small numbers of drug-sensitive bacilli may "persist" despite chemotherapy in full dosage, and start to multiply and spread once dapsone treatment is prematurely stopped. This situation is similar to that which may occur, for example, in typhoid fever, subacute bacterial endocarditis, tuberculosis and brucellosis. The phenomenon of microbial persistence has been particularly well described and discussed by McDermott (1958, 1959). Although reinfection cannot be ruled out in every case, in the great majority indirect evidence favours the recrudescence of the original infection; the time interval after stopping therapy is relatively short, the clinical manifestations of such relapses usually resemble those seen in patients who have developed drug resistance and not those of previously untreated leprosy, and drug-sensitive relapses may occur in lepromatous patients who have emigrated to leprosy free areas.

In the work which we now report, we have investigated the persistence of viable leprosy bacilli in a group of 12 lepromatous patients (LI and LL) who had all received a minimum of 10 years chemotherapy principally or entirely with dapsone. To rule out the possibility of reinfection off treatment, all save one were still receiving dapsone regularly, in a dosage currently varying between 200 mg twice weekly by mouth to 400 mg twice weekly by injection; two patients (nos. 7 and 8) had received dapsone in full dosage twice weekly by injection throughout the ten years. Urine tests confirmed the presence of sulphone.

Our choice of sites for investigation was determined in part by reports of solid bacilli persisting in dermal nerves (Dharmendra, 1960) and smooth muscle (Neves, 1961; Ridley, personal communication, 1962; see also Harman, 1968; Leiker, 1972) and our own experience, clinically with striated muscle (Pearson, Rees and Weddell, 1970, 1973), and experimentally with the mouse footpad and hamster ear infections.

Clinically, all 12 patients appeared to have made a good response to continuous chemotherapy given for 10 to 12.5 years. There was no clinical or histological evidence of mycobacterial activity, although three nerve biopsies, from patients nos. 5, 7 and 11, were suggestive of some continuing tissue damage, probably related to ENL. Patients nos. 7 and 11 still suffered from mild ENL of the skin. This quiescent state of the disease compares favourably with the results reported from Carville (Jacobson and Trautman, 1971), although it must be remembered that in our series the duration of active lepromatous leprosy before the start of treatment was shorter, as was also the period of follow-up; more especially, treatment had been continued in full dosage despite ENL in nine and neuritis in a tenth.

Although the leprosy was quiescent, occasional multiplication has been obtained with 10 of 37 tissue suspensions, from seven of the 12 patients, inoculated into mouse footpads. All four tissue sites have been implicated. Three successful passage experiments have revealed that two strains of *Myco. leprae* (no. 3, skin; no. 5, skin) were without doubt fully sensitive to dapsone, and a third (no. 11, nerve) almost certainly so (although the small number of "takes" in the untreated control mice in the latter experiment prevent absolute certainty). Therefore, here is proof positive that viable drug-sensitive bacilli can persist for a full ten years in treated lepromatous patients. In this connection it is of interest that we have also isolated a dapsone-resistant strain of *Myco. leprae* from the striated muscle of a proven sulphone-resistant patient who had been treated continuously for five years with clofazimine and was still on such treatment.

The few takes obtained per group of mice are compatible with the minute

numbers of *Myco. leprae,* of uncertain viability, which were inoculated. Moreover, we failed to obtain enhancement in T900R mice, and during first and second passage three of six strains died out, a situation quite unlike our experience of strains of leprosy bacilli obtained from patients with active leprosy. McDermott and his colleagues have reported that "persisting" strains of *Mycobacterium tuberculosis* in treated experimental tuberculous infections in mice were considerably more difficult to isolate *in vitro* than ordinary populations of the tubercle bacillus. Indeed, immediately after three months' chemotherapy of experimental tuberculosis using certain drug combinations, it was found impossible to isolate any colonies of *Myco. tuberculosis in vitro*; but if similarly infected and treated mice were left for variable periods after the course of chemotherapy had been completed, then it became increasingly easy to isolate such "persisting" bacilli (McCune *et al.,* 1966; McCune, Feldmann and McDermott, 1966). Probably similar factors apply to strains of *Myco. leprae* persisting in well treated lepromatous patients, and we could well have been fortunate to have obtained any multiplication at all in mouse footpads of bacilli obtained from patients currently receiving such long term therapy. We presume, by analogy with the results of McCune *et al.,* that after stopping chemotherapy prematurely, the leprosy bacilli left alive would slowly regain their capacity to grow, multiply and spread. Certainly, three of the same group of some 80 lepromatous patients from which our volunteers were obtained, who absconded from treatment after seven, eight and nine years respectively, were all found to have relapsed (three histologically and two clinically) when they later returned to Sungei Buloh Leprosarium. Furthermore, also by analogy with McCune *et al.,* negative findings in mice, say after 15 or 20 years of dapsone therapy, would not necessarily indicate that all viable "persisters" had died out.

These preliminary results confirm that small numbers of leprosy bacilli may persist for many years in treated lepromatous patients, and suggest that several tissues are involved. Unfortunately, the histology examined so far does not pin-point precisely in which cell-types these bacilli remain alive, although there is little doubt that nerve is involved. We plan to continue and expand this study, and the bacteriological results of the additional biopsies are still awaited. Nevertheless, a number of important conclusions may already be drawn. For control workers, the seriousness of losing lepromatous patients from control is even more evident, as is also the importance of discovering and diagnosing leprosy at the indeterminate and borderline stages before a proportion of such patients are able to develop lepromatous leprosy—thereby avoiding very long term chemotherapy with all its problems and demands. More especially, the achievement of negative smears in lepromatous leprosy is no guide whatsoever as to the safety or otherwise of stopping antileprosy treatment; dapsone therapy must be continued for many more years than ten, at least in all but very early cases ("L2" and "L3") and with our present knowledge, we prefer to continue giving it for life.

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The Relationship of Dapsone (DDS) Therapy to *Erythema Nodosum Leprosum* Is it Direct or Indirect?

M. F. R. WATERS AND H. S. HELMY*

Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, Selangor, Malaysia

A double-blind, internally-controlled clinical trial is reported of the effect of dapsone on the severity of *erythema nodosum leprosum* (ENL) in 17 sulphone-resistant lepromatous patients, 16 of whom were suffering from ENL of varying severity. During the 10 weeks of the trial, alternative anti-leprosy treatment was continued unchanged. Dapsone, 100 mg daily in a coloured capsule, was prescribed for 14 consecutive days between the third and seventh weeks, the timing being allocated by random distribution, and on the remaining 56 days an identical placebo capsule was given. The clinical severity of the ENL was measured by a number of parameters, and the intake of all reaction-suppressing drugs was recorded. No evidence was obtained that dapsone either immediately or after an interval, exacerbated or precipitated episodes of ENL. It is concluded that dapsone has no direct ENL-stimulating action *per se*, but that ENL results indirectly, consequent on the drug's chemotherapeutic activity against *Mycobacterium leprae*.

It is universally agreed that the introduction of the sulphone group of drugs resulted in a marked increase in the incidence of *erythema nodosum leprosum* (lepromatous lepra reaction, ENL). The commencing of effective treatment sooner or later precipitates ENL in many lepromatous patients. However, the precise mechanism whereby dapsone (DDS) and other proven anti-leprosy drugs predispose patients to, or initiate attacks of, ENL has been little investigated. Two theories have been propounded. The first considered that the relationship was an indirect one; effective chemotherapy results in the death of leprosy bacilli, and subsequently the products of bacterial disintegration are released into the bloodstream or tissues, and cause ENL (Mitsuda, 1953; Pepler *et al.*, 1955). This theory has been supported by studies on the morphology of *Mycobacterium leprae* (Ridley, 1960; Pettit and Waters, 1967). The second theory, or rather group of theories, as there are a number of not very well defined variants, considers that dapsone acts directly on the tissues, and that as a corollary the tissue effect is closely related to the dosage of dapsone employed. Thus Jopling

*Present address: Ministry of Health, Cairo, Egypt
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(1964) stated that a patient suffering from ENL with no known precipitating cause, can be told that, "His tissues have been destroying the leprosy bacilli too rapidly and it is necessary to proceed at a slower tempo; he will then appreciate the reason for reducing the dosage of anti-leprosy drug." Cochrane (1967) suggested that dapsone does not act directly on the leprosy bacillus, but through cell lysosomes; and warned that dapsone in full dosage might push very active lepromatous patients into reactive phases.

It therefore seemed important to us, not only for theoretical but also for practical reasons related to patient management, to investigate whether there was any evidence of a direct relationship between dapsone and ENL *divorced from* its chemotherapeutic activity. Until recently, this was not possible. However, over the past decade, more than 100 proven sulphone-resistant patients have been detected at the Leprosy Research Unit, Sungei Buloh. Therefore, a double-blind, internally-controlled study was devised to investigate the effect of dapsone on the severity of ENL in a group of sulphone-resistant patients, in whom it was assumed that the drug could have no chemotherapeutic action.

Patients and Methods

The design of the trial was based on the methods developed at the Leprosy Research Unit for testing the effect of drugs against established ENL (Pearson and Vedagiri, 1969; Waters, 1971*a*; Helmy *et al*., 1971; Pearson and Helmy, 1973).

Twenty patients were selected from among those regularly attending the Research Unit; three were in hospital wards, 16 were living in quarters within and one lived just outside the hospital grounds. Seventeen were male and three were female; all except one were Chinese. All 20 were suffering clinically from sulphone resistant lepromatous leprosy, and in the 18 in whom inoculation studies were successful, dapsone resistance was confirmed by drug sensitivity testing in mice. All had received effective alternative treatment with rifampicin, rifampicin plus thiambutosine, clofazime, or clofazimine plus rifampicin, for at least three months (range 3-51, average 16 months). The patients were smear positive, with an average bacterial index (BI) of 4.0 (range 2.2 to 5.0); and the morphological index (MI) was 0. All patients gave a history of ENL, and 19 were suffering from reactions of varying severity at the start of the trial, although in half the ENL was mild and intermittent.

The clinical diagnoses of ENL and of lepromatous leprosy were histologically confirmed. Before admission to the trial, patients underwent a complete clinical examination, including assessment of ENL; blood count and urinalysis were performed, and the urine was checked for dapsone content. Skin smears were taken, unless they had been examined within the previous three months, and lepromin and tuberculin skin tests were carried out, unless they had been performed within the previous year.

Design of the Trial

The trial lasted ten weeks. Throughout this time, patients continued on their anti-leprosy treatment in unchanged dosage, including the four receiving clofazimine (two on 200 mg daily, and two on 100 mg twice or thrice weekly respectively). Dapsone was given in the form of a single, coloured capsule containing 100 mg of drug, daily for 14 days, commencing either on day 15, 22,

29 or 36. Allocation was by random distribution using the sealed envelope technique (Waters *et al.*, 1967), and five patients commenced dapsone on each of the four possible days. The doctor in clinical charge (H.S.H.) was kept in ignorance of the dates until the trial was completed and the results tabulated. For the remaining 56 days of the trial, each patient received one placebo capsule, identical with the dapsone capsule, daily. Therefore the double-blind trial was divided into three periods as follows:

Period 1—Initial control period of at least two weeks' duration (range 2-6)—one placebo capsule daily.
Period 2—Dapsone period of two weeks—100 mg dapsone daily.
Period 3—Final control period of at least three weeks' duration (range 3-6)—one placebo capsule daily.

During all periods of the trial, the patients attended the Research Unit twice weekly at about 2 p.m., to have their temperatures taken, to undergo clinical examination, and to swallow (and be seen to swallow) the appropriate day's capsule. The next two, or three, days' capsules were issued to the patients to take in their quarters. Each patient was examined by the same doctor throughout, who recorded the severity of the ENL on a sheet specially prepared for each day (without reference to past records), noting the number of paracetamol, prednisolone and thalidomide tablets, clofazimine capsules and stibophen and corticotrophin injections consumed or received since his or her last visit. Regularly every two weeks urine was tested for the presence of dapsone, and white blood cell and differential counts were performed. At the end of the trial period, the complete clinical examination was repeated.

Although all clinical examinations were carried out blind by a single doctor (H.S.H.), as a check on his scoring each patient was examined by an independent clinical assessor before admission to the trial and, at a time unbeknown to him, during the second week of dapsone therapy. Throughout the trial, the doctor in clinical charge was free to prescribe anti-reaction treatment as he considered indicated by the condition of each individual patient.

Methods of Scoring

On each examination the severity of a patient's ENL was categorized under seven headings, listed and scored according to Table 1. The latter also gives the method of scoring (allocation of numerical values) of the two objective assessments, namely the temperature and the white blood count. With experience gained from our previous trials it is considered that the subjective but important assessments of ENL severity and the pattern of prescribing anti-reaction treatment were consistent and reproducible so that meaningful comparisons could be made.

In the current trial, no attempt was made to equate the score of one clinical feature with another. Rather, the individual and group scores for each parameter have been totalled for each week (centred around the fortnight in which dapsone was administered) to assess if dapsone increased, decreased or had no effect on the severity of ENL in these specially selected patients. The scores have also been compared with the totals of the different anti-reaction treatments prescribed and taken, as increased effective treatment should result in decreased clinical severity of ENL if no absolute change in severity has occurred and vice versa. Similarly, alterations in reaction severity should be reflected either in corresponding

TABLE 1

Clinical grading of ENL and scores allotted for different parameters on each twice-weekly examination.

Score	ENL (Skin) Lesions		Nerve involvement	Lymph nodes	Eyes	Testes	Arthritis	Maximum temperature recorded	Total white blood cell count[a]
	Number	Activity							
0	None	–	None	Not enlarged	Not inflamed	No orchitis	No ENL arthritis	Below 99°F	0-9900
1	Few	Mild	1 tender	Enlarged, none tender	Conjunctivitis or iritis present	Orchitis present	ENL arthritis present	99°-98[8]	10,000-13,900
2	Moderate number	Moderately active	More than 1 tender	Enlarged, one or more tender	–	–	–	100°-100[8]	14,000-17,900
3	Many	–	1 nerve painful	–	–	–	–	101° or over	18,000 or more
4	–	Very active, some ulcerating and/or forming pustules	More than 1 painful	–	–	–	–	–	–

[a]White blood cell count performed every fortnight.

alterations in observed clinical severity, or in appropriate changes in total treatment prescribed, or both.

Results

Although all 20 patients completed the trial, three have been omitted from the analyses, two because their urine failed to contain dapsone when it should, and one because his urine contained dapsone when the drug was not being prescribed.

In the remaining 17 patients, one (who had received only five months effective treatment for sulphone-resistant leprosy) did not suffer from ENL throughout the trial, although variable non-tender enlargement of her lymph nodes was recorded, and was considered to be a prodromal sign of ENL, which recurred shortly afterwards. A study of the individual results of the 16 patients suffering from ENL reveals only minor variations in reaction severity, consistent with the known natural variations occurring in ENL reactions. Table 2 gives the overall results (total weekly scores, i.e. aggregate of both twice-weekly examinations) for the 17 patients for the two weeks before, two weeks of, and the three weeks immediately succeeding the giving of daily dapsone; the table includes the scores

TABLE 2

Effect of dapsone, 100 mg daily for two weeks on the clinical severity of ENL in 17 sulphone-resistant lepromatous patients—total weekly scores for the two weeks immediately before, the three weeks following and the fortnight of dapsone administration

	Before dapsone (weeks)		Dapsone period (100 mg daily) (weeks)		After dapsone (weeks)		
	2	1	1	2	1	2	3
ENL skin lesions:							
(a) number	22	26	21	17	19	25	21
(b) activity	18	21	16	12	17	18	21
Nerves	14	7	14	21	16	13	13
Lymph nodes	14	16	14	12	12	16	20
Eyes[a]	2	2	2	1	1	1	0
Testis[b]	0	0	0	0	0	1	0
Arthritis	1	0	1	0	0	0	0
Temperature	0	2	0	4[d]	3	6[d]	2
White blood count[c]		5		8[d]		6[d]	

[a] Based on 16 patients, as one was blind from past iritis.
[b] Based on 14 patients (3 were female).
[c] Fortnightly examinations.
[d] These figures were influenced by factors additional to ENL (see text).

of the seven measured individual clinical parameters of ENL severity, plus temperature and white blood count assessments. These results should be interpreted in conjunction with those of Table 3, which gives details of total anti-reaction treatment prescribed and taken each week during the same periods. Seven patients received only paracetamol and/or stibophen, eight required thalidomide with or without paracetamol and stibophen (two of these were also receiving clofazimine, in low dosage), and two received high dosage clofazimine, one also requiring daily prednisolone. In interpreting the paracetamol intake, allowance must be made for two patients whose dosage was temporarily increased, twice each, for reasons other than ENL, including two episodes of

TABLE 3

Effect of dapsone, 100 mg daily for two weeks on the severity of ENL in 17 sulphone-resistant lepromatous patients—total weekly dosage of ENL-suppressing drugs given during the two weeks immediately before, the three weeks following, and the fortnight of dapsone administration.

ENL treatment	Before dapsone (weeks)		Dapsone period (100 mg daily) (weeks)		After dapsone (weeks)		
	2	1	1	2	1	2	3
Thalidomide (no. of 100 mg tablets)	62½	54	52	52½	54	45½	40
Clofazimine (no. of 100 mg capsules)	33	33	33	33	33	33	33
Prednisolone[a] (mg)	52½	47½	37½	57½	52½	52½	52½
Stibophen (ml)	14	16	6	8	10	4	4
Paracetamol[b] (no. of tablets)	112	97	105	142	113	83	114

[a] One patient only received prednisolone, and none corticotrophin during these seven weeks.
[b] Paracetamol intake was influenced by factors additional to ENL (see text).

cellulitis, a mild virus infection and a painful biopsy site. It is concluded that in no patient did the ENL significantly worsen as a result of dapsone intake nor was ENL precipitated by dapsone in the one patient in the prodromal stage of reaction. This is confirmed by the results given in Tables 2 and 3, which reveal no evidence, either from the intake of reaction-suppressing drugs, or from the clinical severity of the ENL, of any increase in ENL severity, either during the two weeks of dapsone administration or in the immediately succeeding three weeks.

Discussion

The 17 patients included in this trial showed a wide range of reaction severity. Six were suffering from mild ENL, and one from prodromal ENL, and they were easily controlled by analgesics and/or stibophen. Ten were more severe, eight requiring daily thalidomide and two clofazimine, in one case combined with daily prednisolone, to control adequately the clinical signs of reactions; even so, two patients experienced short episodes of ulcerating or pustular ENL during the trial. Therefore if dapsone possessed any direct ENL-stimulating effect, as opposed to its chemotherapeutic effect on *Myco. leprae*, we could confidently have expected to be able to detect such an action in this group of sulphone-resistant patients. The trial was designed to include not only the abrupt starting of 100 mg dapsone daily—a dose widely considered to be sufficient to precipitate or exacerbate ENL in many reaction-prone patients—but also a second control period of at least three weeks' duration. The latter enabled us to investigate any delayed dapsone effect, such as appeared to occur in the third and fourth weeks after restarting dapsone in sulphone-sensitive, moderately severe ENL patients (Pearson and Helmy, 1973). No immediate or delayed effect was detected. Therefore we conclude that dapsone produces or stimulates ENL in lepromatous patients only indirectly, as a consequence of the death of *Myco. leprae* resulting from the drug's effective chemotherapeutic action.

This conclusion is in keeping with recent studies on the aetiology of ENL, which has been shown to be an immune-complex disease, comparable to the Arthus phenomenon in experimental animals. Immunoglobulin (IgG) and complement have been demonstrated in ENL skin lesions (Wemambu *et al.*, 1969; Waters *et al.*, 1971), and immune complexes have been detected in lepromatous sera (Rojas-Espinosa *et al.*, 1972), especially in those patients suffering from ENL (Moran *et al.*, 1972; Gelber *et al.*, 1973). Turk and his colleagues have suggested that the antigen moiety of the immune complex may be a soluble, cytoplasmic (not surface) mycobacterial antigen released from dead leprosy bacilli. Why some lepromatous patients remain free of ENL despite long periods of effective treatment, whereas others develop reactions of varying degrees of severity remains speculative; possibly only in a proportion of patients do such antigen-antibody ratios occur which result in the formation of immune complexes capable of producing ENL. Other techniques have been developed to enable further studies to be undertaken, both on the immune complexes themselves, and on the isolation and identification of the mycobacterial-antigen component, and their results are awaited with interest.

If the relationship between ENL and dapsone is an indirect one, dependent on the drug's chemotherapeutic activity, why, as a number of workers maintain, is there any correlation between dapsone dosage and the incidence and severity of reactions? In a series of papers, both Shepard and Rees and their respective colleagues have shown that the minimal effective dose (MED) of dapsone for mice infected with wild strains of *Myco. leprae* is 0.0001% DDS in the diet, and that this MED gives a dapsone serum concentration (minimal inhibitory concentration, MIC) in mice of the order of 0.01 μg/ml (see Ellard *et al.*, 1971). Waters *et al.* (1968) reported that 1 mg dapsone given daily by mouth to seven previously untreated lepromatous patients for 4.5 to six months resulted in a full normal clinical rate of response, with the smear MI falling to zero, or close to zero within 4.5 months. The one patient who elected to remain on 1 mg dapsone daily for a

prolonged period, subsequently developed ENL (Waters and Rees, in preparation). Serum concentrations in the seven patients averaged 0.018 μg/ml, 3 h after taking 1 mg dapsone (Ellard *et al.*, 1971). Therefore both from clinical proof, and by analogy with mice, as little as 1 mg dapsone daily is above the MED and produces serum levels above the MIC in man. This in turn would suggest that any dose of dapsone from 1 mg upwards, resulting as it does in death of leprosy bacilli, would predispose a drug-sensitive lepromatous patient to ENL. Furthermore the precise dose of dapsone prescribed, provided it was above the MED, should have little or no effect on the overall incidence or severity of the resulting reactions in a group of patients. In an admittedly uncontrolled study, we were unable to find any difference over the course of one year in the incidence or severity of ENL developing in two groups of previously untreated lepromatous patients, one receiving 50 mg dapsone twice weekly by mouth, and the other 300 mg dapsone twice weekly by injection (Waters, 1968). However, a number of other authors have maintained, also on apparently uncontrolled data, that in general the higher the dose of dapsone prescribed the higher the incidence of ENL. Some have reported that certain patients appear to have a "trigger" or "threshold" level of dapsone, and dosage above this level invariably leads to episodes of ENL. Moreover, it is authoritatively recommended, for example by the WHO Expert Committee on Leprosy, Third Report (1966), that treatment with dapsone should be suspended when signs of reaction develop, and that after these have subsided, the drug should only be restarted in small dosage. To settle the controversy, a prospective, controlled, preferably double-blind trial of the incidence and severity of ENL in groups of previously untreated lepromatous patients receiving different dosages (above the MED) of dapsone, would appear justified. But low dosage, like irregular dosage of dapsone, has recently been shown to result in an increased incidence of dapsone resistance (Jacobson, 1973; Meade *et al.*, 1973). With the introduction of thalidomide and of clofazimine, we consider that ENL is of less danger to lepromatous patients than the possible development of sulphone resistance. Therefore the onus is on those who advocate low dosage dapsone as producing less ENL, to give scientific proof that their view is correct. For ourselves, we continue to advocate the maintenance of dapsone, in full, uninterrupted dosage, in the treatment of patients suffering from ENL (Waters, 1968, 1971*b*), and the trial now reported gives further support to this view.

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The Pharmacology of Sulphetrone and Its Implications in Sulphone Resistance

ROBERT H. GELBER*

H. C. GOOI

M. F. R. WATERS

Leprosy Research Unit, National Leprosy Control Center, Sungei Buloh, Selangor, Malaysia

and

R. J. W. REES

Laboratory for Leprosy and Mycobacterial Research, National Institute for Medical Research, Mill Hill, London NW7 1AA

Spectrofluorometric techniques were utilized to quantitate dapsone (DDS) and N^4-acetyldapsone (MADDS) contamination of a sulphetrone preparation used for leprosy in Malaysia between 1947 and 1951. Also plasma levels of DDS and MADDS following administration of a standard intramuscular dose of this preparation were studied. The preparation was contaminated with trace amounts of DDS but no MADDS. Following injection the plasma levels were substantial and suggested that sulphetrone was converted *in vivo* to DDS. The importance of these findings to the problem of sulphone resistance is discussed.

Introduction

Sulphetrone (solapsone), a sulphone, was prepared in 1936 (Buttle *et al.*, 1938) and subsequently attracted attention because of its antituberculosis activity (Brownlee and Kennedy, 1948) and low toxicity (Brownlee, 1948). Sulphetrone was first shown to be effective in the treatment of lepromatous leprosy in 1942 (Harkness and Brownlee, 1948) and was widely used for some 12 years (Dharmendra, 1950; Cochrane *et al.*, 1949; Austin, 1950). However, it fell into disrepute because it is poorly absorbed in the gastrointestinal tract (Smith, 1949*a*), causes pain following intramuscular injection, and was thought to act

* Request reprints from Robert H. Gelber, Chief, Infectious Diseases, United States Public Health Service Hospital, 15th Ave. and Lake St, San Francisco, California 94118 U.S.A.
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against *Mycobacterium leprae* only because of contamination with dapsone (DDS) (Lowe, 1952) or conversion *in vivo* to it (Smith, 1959*b*). Deavin *et al.* (1967), utilizing a semiquantitative assay, demonstrated that sulphetrone was contaminated with 0.5-2% DDS.

A recent retrospective analysis by Meade *et al.* (1973) of the emergence of sulphone resistance among lepromatous leprosy patients at the National Leprosy Control Center, Sungei Buloh, Malaysia, showed an incidence of 8% in patients initially treated between 1947 and 1951 with sulphetrone, compared to an incidence of 2% in patients begun on DDS. Highly sensitive and specific spectrofluorometric techniques for the assay of DDS and its monoacetyl metabolite (MADDS) have now been developed (Peters *et al.*, 1970). We applied these methods to determine the amount of DDS and MADDS in the same sulphetrone preparation used earlier in Malaysia and also to determine plasma concentrations obtained in patients following the usual therapeutic dose of this preparation. It was hoped that information from these studies might prove useful in assessing the efficacy of other sulphone preparations, as well as different DDS regimens.

Methods

Two vials of aqueous 30% sulphetrone (Ph Lab Kuala Lumpur) were diluted serially with distilled water to 1/2500 and 1/5000, and the concentrations of DDS and MADDS determined fluorometrically (Peters *et al.*, 1970) in duplicate samples. This method was modified to avoid sulphetrone breakdown by omitting sodium hydroxide during the initial extraction.

Eight adult patients volunteered to discontinue all sulphones for two weeks. After this period a baseline urine was analysed for sulphone content by a modification of the procedure of Bratton and Marshall (1939), sensitive to 0.3 μg/ml. Five ml of the 30% sulphetrone preparation was then injected intramuscularly, and heparinized plasma was obtained generally just before and 4, 8, 24, 48, 72 and 96 h after administration. Plasma concentrations of DDS and MADDS were determined fluorometrically. No specimens were studied after four days because in Malaysia the standard practice had been to treat leprosy patients with 5 ml sulphetrone twice weekly.

Results

There was no (0.02 mg/ml) MADDS found in either of the two vials of sulphetrone studied. Duplicate specimens and at the two dilutions studied showed no greater than 1% discrepancy in the amount of DDS contamination of the sulphetrone preparation. DDS concentration in the two vials was 0.70 and 0.75 mg/ml.

Plasma levels of DDS and MADDS following a single intramuscular injection of sulphetrone in each of the eight patients studied are presented in Table 1.

Discussion

These studies confirm that sulphetrone is contaminated with trace amounts of DDS. The average plasma DDS concentrations found in subjects 24 and 48 h after sulphetrone administration were 93 and 78 mg/ml respectively. Twenty-four and 48 h after a 50-mg oral dose of DDS in patients from this institution, the mean

TABLE 1

MADDS and DDS plasma levels following intramuscular administration of 5ml 30% sulphetrone

Patient (Wt in kg)	Substance	Plasma concentration (mg/ml) Hours after injection 0	4	8	24	48	72	96
Indian male	DDS	–	90	80	100	80		30
(58.2)	MADDS	–	20	20	20	20		10
Chinese female	DDS	0	100	90	120	120		100
(40.9)	MADDS	0	70	70	120	120		80
Chinese male	DDS	10	90	90	70	70		
(60.0)	MADDS	10	50	50	40	40		
Chinese male	DDS	10	60	60	60	40	30	10
(48.2)	MADDS	20	70	60	50	50	30	20
Chinese male	DDS	10	70	70	70	70	40	20
(53.2)	MADDS	30	40	50	30	30	30	20
Malay male	DDS	0	–	–	90	60	30	20
(52.0)	MADDS	0	–	–	10	10	0	0
Malay male	DDS	10	–	–	120	110	100	80
(48.0)	MADDS	20	–	–	60	50	50	30
Chinese male	DDS	0	–	–	110	70	40	20
(48.0)	MADDS	0	–	–	80	50	30	20
Average	DDS	6	82	78	93	78	48	40
	MADDS	11	50	50	51	46	28	26

Tests for urinary DDS concentration, sensitive to 0.3 μg ml, were negative for all patients before injection of sulphetrone.

plasma levels were 260 and 128 mg/ml respectively (Gelber and Rees, unpublished results). Since plasma concentration of DDS has been found to be linearly related to dose (Ellard *et al.*, 1971), certainly the 3.5 or 3.75 mg DDS contaminating each sulphetrone injection is too little to account for the circulating levels of DDS. Hence significant *in vivo* metabolism of sulphetrone to DDS must occur.

Patients treated with the intramuscular repository sulphone acedapsone (DADDS) in the usual dose of 225 mg every 77 days averaged 25 to 31 mg/ml DDS in the plasma just before the next injection (Murray *et al.*, in press; Gordon *et al.*, in press). As plasma levels of DDS in patients treated with sulphetrone in Malaysia on the average would not have fallen below 40 mg/ml, DADDS therapy of bacilliferous leprosy might similarly result in an unacceptable frequency of relapse with DDS-resistant *Myco. leprae*. We therefore would be reluctant to recommend DADDS as monotherapy of lepromatous leprosy in areas where other alternatives are possible.

It has been demonstrated that 1-10 mg/ml DDS in plasma will prevent multiplication of *Myco. leprae* in the footpads of mice (Shepard *et al.*, 1969; Ellard *et al.*, 1971) and rats (Peters *et al.*, 1972). Patients treated with sulphetrone maintained levels that were at all times above this minimal inhibitory concentration, and yet 8% of them relapsed with dapsone-resistant leprosy, which must be considered unacceptable. Thus it may be hazardous to extrapolate from levels of dapsone effective for preventing multiplication in the local self-limited infection in mice and rats to the treatment of the severe and progressive systemic disease that *Myco. leprae* may cause in man, because of differences in bacterial load and hence the numbers of DDS-resistant mutants. Results from this study suggest that the currently fashionable low-dose DDS regimens may be hazardous.

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Gut Amyloidosis in Lepromatous Leprosy Regressing with Therapy

R. R. GRIGOR, W. R. LANG and G. I. NICHOLSON

Departments of Gastroenterology and Infectious Diseases, Auckland Hospital, New Zealand

Two Samoan patients with gut amyloidosis secondary to lepromatous leprosy were studied for five years. Intestinal "pseudo-obstruction" and malabsorption were prominent early features. Evidence suggesting regression of the amyloid deposits following control of the leprosy included clinical, biochemical, radiological and histological data.

Introduction

Lepromatous leprosy may be complicated by amyloidosis. When gastrointestinal amyloidosis occurs, malabsorption and "pseudo-obstruction" may be serious clinical features (Gilat and Spiro, 1968). Regression of amyloid in patients has only occasionally been documented before, when improvement of secondary amyloidosis has followed therapy directed at the underlying disease (Triger and Joekes, 1973).

A five year study of two patients with lepromatous leprosy complicated by amyloidosis of the gastrointestinal tract causing malabsorption and "pseudo-obstruction" is reported. The follow up data suggest regression of the amyloid.

Case Reports

CASE 1

Mrs J. B. was diagnosed as having leprosy in Samoa in 1944 when aged 21. She received 12 years of chemotherapy on Makogai Island. She came to New Zealand in 1959. Lepromatous leprosy was confirmed in Auckland by skin biopsy in 1963, and because she was considered infectious she underwent six years hospitalisation. Treatment with dapsone, thiambutosine, and clofazimine was given.

Four years after admission she gradually developed weight loss, cachexia and weakness. At this time skin biopsy specimens were submitted for mouse inoculation testing and *Myco. leprae* resistant to dapsone were reported. Treatment with dapsone was stopped.

In 1968 a faecal fat excretion exceeding 50 g daily on a ward diet confirmed malabsorption. Other laboratory investigations included calcium 5.2 mg/100 ml, albumin 0.9 g/100ml, prothrombin clotting time less than 5%, "flat" glucose tolerance curve, and *d*-xylose, and vitamin B12 (Schillings) absorption tests at the

lower limit of normal. Gross indicanuria was present. Amyloid deposition was found in the lamina propria of a rectal biopsy, but not in a per-oral jejunal mucosa biopsy or in a needle biopsy of the liver.

Intermittent, but increasingly frequent and severe episodes of colicky abdominal pain and post-prandial vomiting occurred. A barium series revealed grossly impaired small bowel peristalsis (Fig. 1). A laparotomy was performed, but showed no evidence of a mechanical obstruction. The stomach and duodenum felt thickened, but the large bowel, liver, spleen, pancreas and kidneys were macroscopically normal. Sirius staining of jejunal biopsy specimens demonstrated large deposits of amyloid in the lamina propria and in the walls of submucosal vessels (Fig. 2). Vessel wall deposition was also seen in the appendix and liver.

Drug malabsorption was suspected and the dose of clofazimine was increased from 600 mg/week to 600 mg/day. Doxycycline 200 mg/day was added for its postulated antilepromatous effect (Opromola *et al.*, 1970) and to control the bacterial invasion of the upper small bowel which was probably causing the indicanuria. Over the next five months a marked improvement in gastrointestinal symptoms and general condition was noted. Nasal septum and skin smears became negative, enabling discharge from hospital. Within a year, faecal fat excretion was reduced to 6 g/day and the radiological appearance of the small bowel was

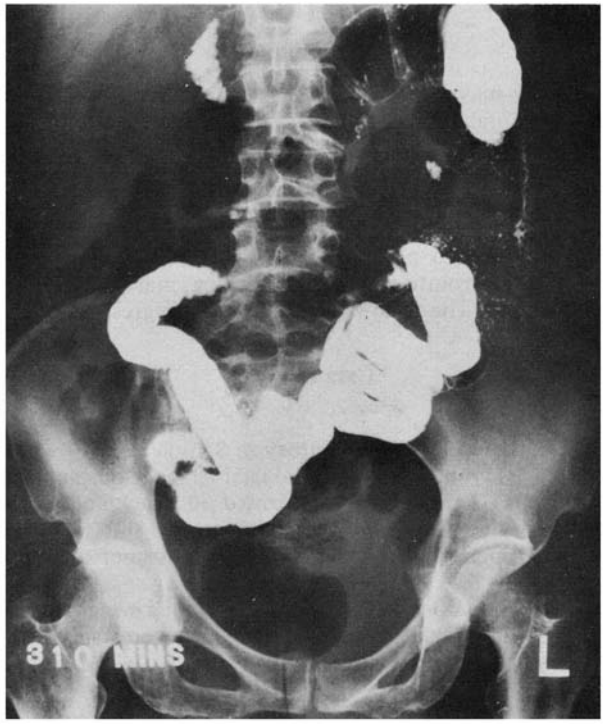

Fig. 1. (Case 1.) Barium small bowel X-ray at 5 h shows grossly impaired small bowel peristalsis. (24 June 1968.)

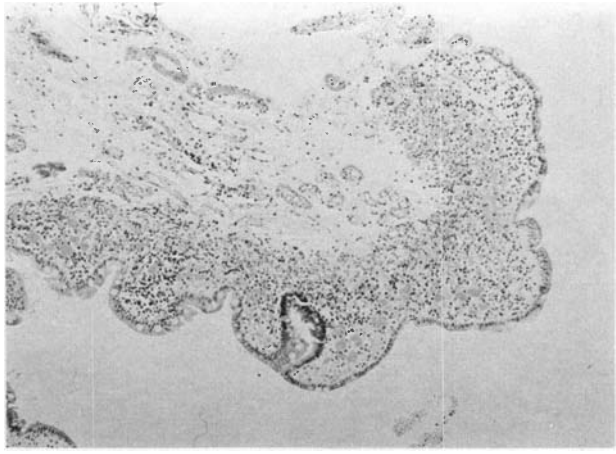

Fig.2.(Case 1.) Jejunal biopsy obtained at laparotomy. Large deposits of amyloid are shown in the lamina propria and in the walls of the submucosal vessels (sirius stain). (27 June 1968.)

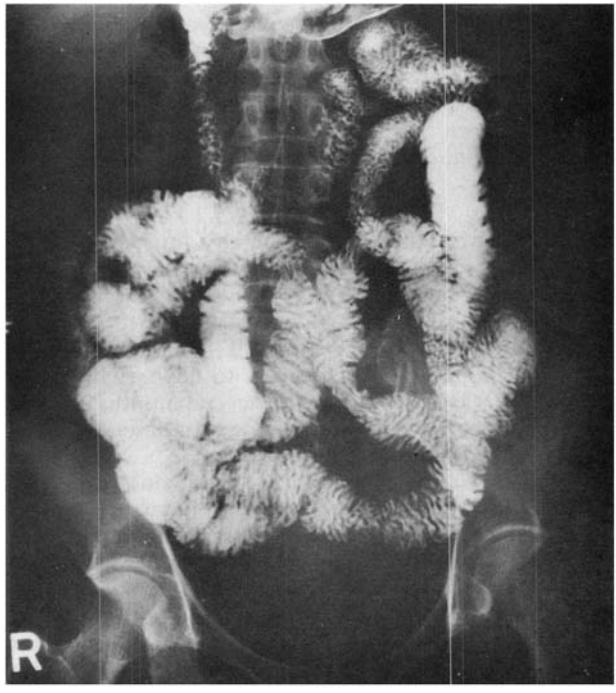

Fig.3.(Case 1.) Barium small bowel X-ray at 30 min. Following three years of effective treatment of the leprosy, the tracing is now within normal limits. (30 April 1971.)

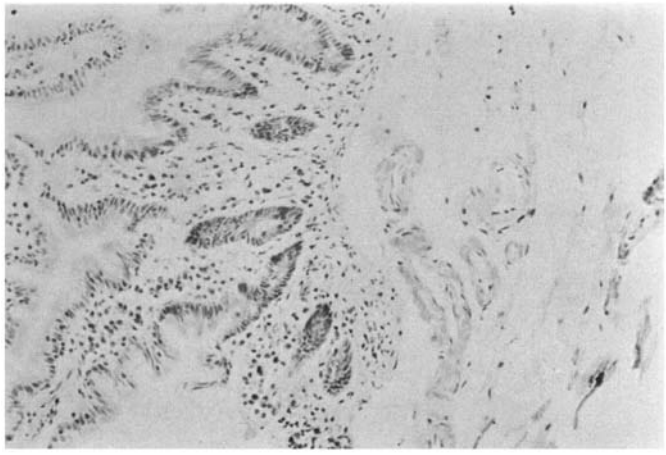

Fig.4.(Case 1.) Per-oral jejunal biopsy. The amount of amyloid deposition has decreased following three years of effective treatment of the leprosy (sirius stain). (6 May 1971.)

improved. Three years following discharge, she remained free from bowel symptoms. Faecal fat excretion and small bowel X-rays were normal (Fig. 3). A random per-oral jejunal mucosal biopsy showed a smaller amount of amyloid deposition than had been present in the surgical specimen (Fig. 4). The clofazimine has now been stopped, but she continues to take rifampicin 600 mg/day and doxycycline 200 mg/day.

CASE 2

Mr A. C. has had intermittent dapsone therapy for leprosy in Western Samoa since aged 15 years. He presented in Auckland with the cutaneous manifestations of lepromatous leprosy when aged 24, in 1968. There were minimal systemic symptoms. Dapsone and clofazimine were prescribed but positive smears containing solid staining organisms were still being obtained even after the addition of rifampicin. Some doubt existed as to how reliably he was taking his medication. In 1971 he was readmitted with several months' intermittent colicky abdominal pain and post-prandial vomiting. He also described four to five loose bowel motions/day. Weight loss had been three stone.

On examination, he was cachetic with finger clubbing and tetany. Mild hepatomegaly, slight abdominal distension and increased bowel sounds were present. There was laboratory confirmation of malabsorption; faecal fat excretion was 12 g/day on a ward diet, serum calcium 5.2 mg/100 ml, albumin 1.2 g/100 ml, prothrombin clotting 37%, "flat" glucose tolerance curve, and impaired *d*-xylose absorption. A plain abdominal X-ray showed fluid levels and gas in both small and large bowels (Fig. 5). A barium X-ray of the small bowel demonstrated delayed transit time, dilated loops of proximal jejunum, areas of segmental narrowing and coarsening of the mucosal folds (Fig. 6). A per-oral jejunal mucosal biopsy showed amyloid deposition in the deeper layers of the lamina propria, particularly round vessels in the submucosa (Fig. 7). Jejunal disaccharidase deficiency was also demonstrated.

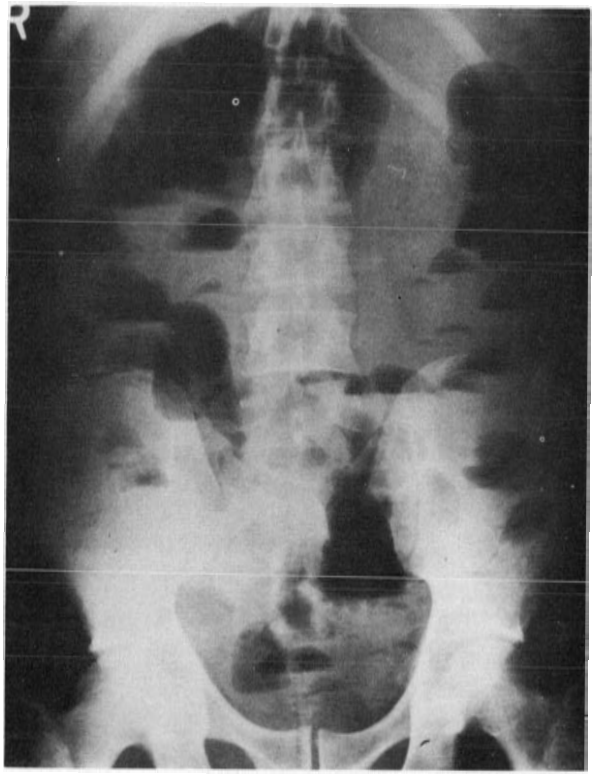

Fig.5.(Case 2.) Plain X-ray of abdomen shows fluid level and gas in both small and large bowels. Serum electrolytes were normal. (29 March 1971.)

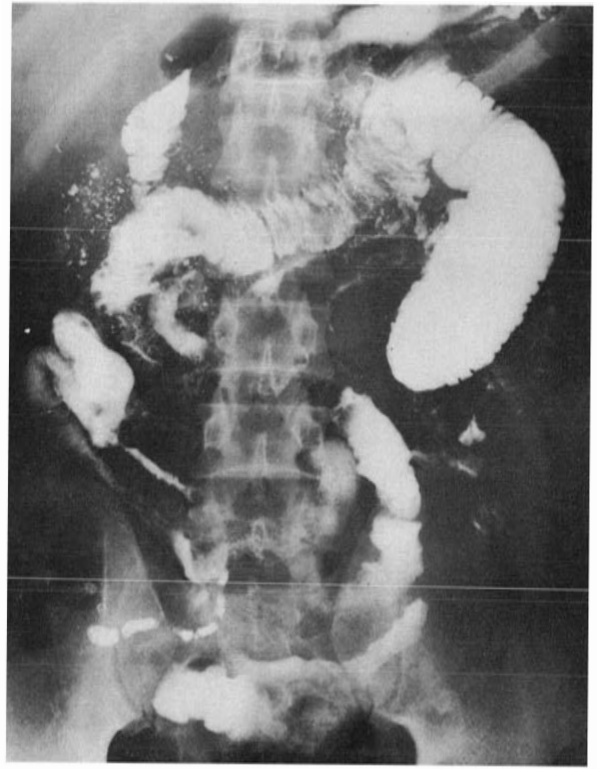

Fig.6.(Case 2.) Barium small bowel X-ray at 3 h demonstrates delayed transit time, dilated loops of proximal jejunum, areas of segmental narrowing, and coarsening of mucosal folds. (5 March 1971.)

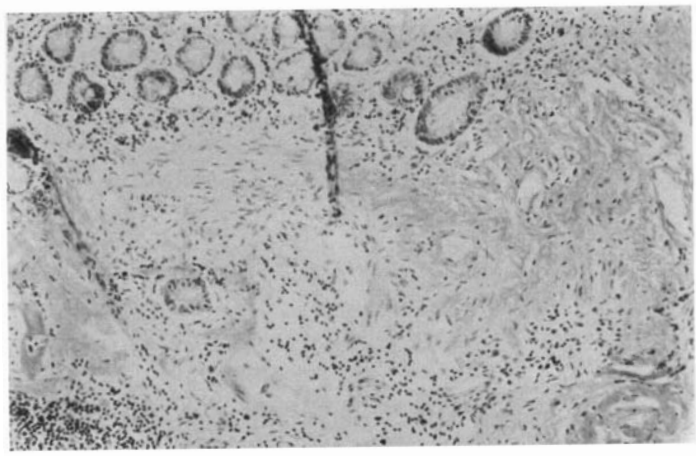

Fig.7.(Case 2.) Per-oral jejunal mucosal biopsy. Amyloid deposition in the deeper layers of the lamina propria, particularly around vessels in the submucosa (sirius stain). (8 March 1971.)

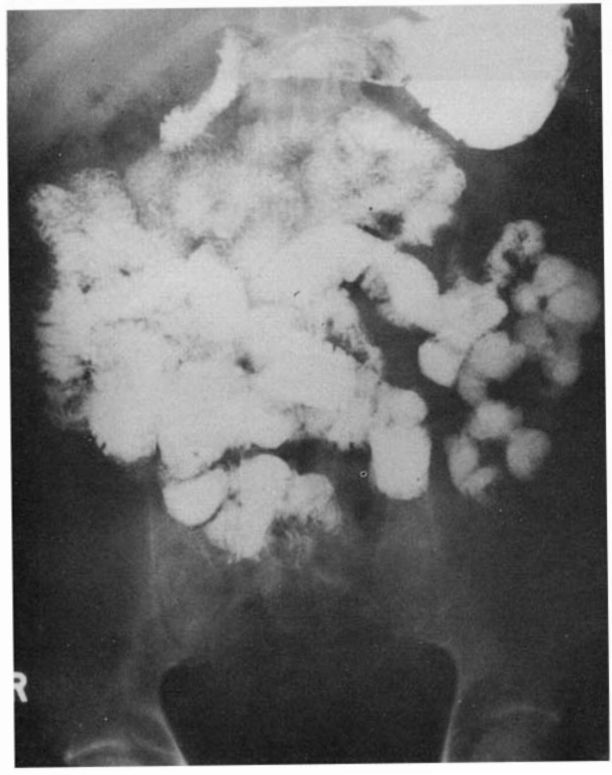

Fig.8.(Case 2.) Barium small bowel X-ray at 15 min. Following more intensive treatment of the leprosy for 18 months, the tracing is now within normal limits. (30 August 1972.)

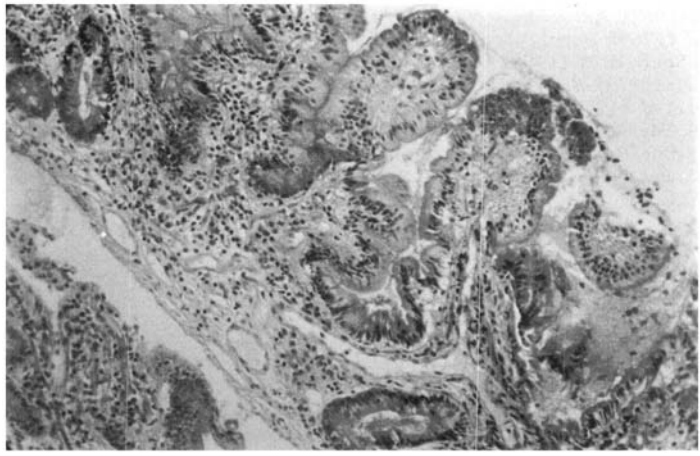

Fig.9.(Case 2.) Per-oral jejunal biopsy. The amount of amyloid deposition has decreased following 18 months effective treatment of the leprosy. (31 August 1972.)

The "pseudo-obstruction" syndrome was diagnosed and managed conservatively with intermittent intravenous therapy for two months. In view of the malabsorption, the dose of antilepromatous drugs was increased, and he was started on a "triple" regime of clofazimine 600 mg/day, rifampicin 1200 mg/day, and doxycycline 200 mg/day. There was gradual clinical improvement and one year later he had no gastrointestinal symptoms and no clinical or laboratory evidence of malabsorption. Barium X-rays of the small bowel were normal (Fig. 8). A repeat per-oral jejunal biopsy showed less amyloid deposition in the bowel wall than previously (Fig. 9). He continues to take a reduced dose of clofazimine, rifampicin and doxycycline. His smears for leprosy bacilli remained negative.

Discussion

Amyloidosis is a well-described complication of lepromatous leprosy (Beddow and Tilden, 1960; Cohen, 1967; Gilat *et al.*, 1969). Malabsorption and the "pseudo-obstruction syndrome" are recognized manifestations of amyloidosis involving the gut (Gilat and Spiro, 1968; Legge *et al.*, 1970). The diagnosis of pseudo-obstruction and its management by conservative means is important, as surgery is hazardous in these patients who are often critically ill (Legge *et al.*, 1970; Leading Article, *British Medical Journal,* 1973).

It is suggested that regression of the gut amyloidosis has occurred in these two patients. The clinical, biochemical and radiological data showed definite improvement following more effective treatment of the underlying leprosy. Although the comparison of small serial biopsies is complicated by sampling problems, there is also some histological evidence of regression.

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SGOT, SGPT and Hepatitis B Antigen in Leprosy

S. S. KELKAR

Department of Microbiology, Medical College, Aurangabad, India

K. B. NIPHADKAR

Department of Microbiology, B. J. Medical College, Poona, India

P. M. KHARE

Department of Pathology and Bacteriology, B. J. Medical College, Poona, India

and

P. V. KASBEKAR

Sassoon General Hospitals, Poona, India

Serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) levels were determined in seven cases of tuberculoid leprosy carrying hepatitis B antigen (HB-Ag) and compared with the levels in 50 HB Ag-negative cases of tuberculoid leprosy. The mean value for SGPT and SGOT in the former group was 7.86 and 8.86 IU/L respectively, while in the latter it was 9.08 and 11.48 respectively. Similarly the mean values for SGPT and SGOT in eight HB Ag-positive cases of lepromatous leprosy were 8.88 and 13.75 IU/L respectively while the mean figures for 50 HB Ag-negative cases of lepromatous leprosy were 7.96 and 12.48 IU/L respectively. The differences obtained in lepromatous leprosy were statistically insignificant. There was no difference in the serum enzyme levels of HB Ag-positive and negative cases and the range of values obtained were comparable. The absence of liver damage as indicated by enzyme studies suggests the host-parasite relationship of the hepatitis B virus in leprosy to be one of symptomless carriage.

Introduction

Hepatitis B antigen (HB-Ag), a surface antigen of the Hepatitis B virus, occurs more frequently in sera of patients with leprosy than in the normal populations (Blumberg *et al*, 1967; Blumberg and Melartin, 1970*a*). The interaction between man and this virus shows an intriguing variety of host-parasitic relationships which

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range from symptomless carriage, through mild chronic liver injury which can lead to cirrhosis of the liver to the explosive attack of acute viral hepatitis (Sherlock *et al*, 1970). Carriage of HB antigen in leprosy is possibly of two types (1) harmless carriage and/or (2) associated with mild hepatic damage. Blumberg and Melartin (1970*b*) studied liver function in 28 cases of lepromatous leprosy carrying HB antigen and found that only the SGPT levels, though often in the normal range, were significantly higher than those in a similar number of leprosy patients not carrying the antigen. The inference was that the hepatitis B virus caused mild liver injury. Post-mortem studies in the literature, however, do not record cirrhosis of the liver to be a common occurrence in patients with leprosy (Kean and Childress, 1942). This rarity of cirrhosis suggests that HB antigen carriage is not frequently associated with chronic liver injury.

We have had occasion to study HB antigen carriage in a large series of leprosy patients (Kelkar *et al.*, 1973*b*). During these studies, SGPT and SGOT levels of some of the patients with and without HB antigen were estimated, with a view to investigate the nature of the host-parasitic relationship of the hepatitis B virus carriage in patients with leprosy.

Material and Methods

The patients consisted of seven with tuberculoid and eight with lepromatous leprosy all of whom had HB antigen in their sera. For a comparison, 50 patients with tuberculoid and 50 with lepromatous leprosy and not carrying the HB antigen, were studied. Sera from these patients were tested for SGOT and SGPT levels by the method of Reitman and Frankel (1957). Detection of HB-Ag was done by both agar gel double diffusion and a counter immunoelectrophoretic technique (Kelkar *et al.*, 1974; Kelkar *et al.*, 1972).

Results

Figures 1 and 2 are scatter diagrams illustrating the values for SGPT and SGOT obtained in the patients studied. Table 1 gives the mean figures for the different groups as well as the numbers of cases showing raised enzyme levels. The accepted upper normal limits for SGPT and SGOT are 15 and 20 IU/L respectively

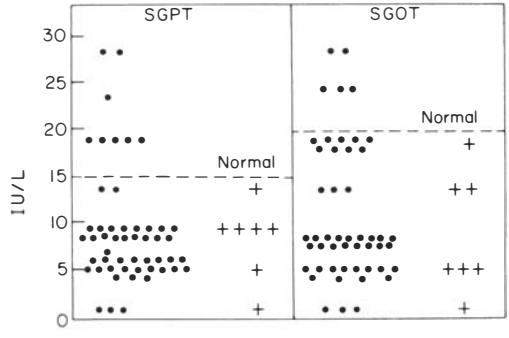

Fig.1. Scatter diagram showing SGPT and SGOT levels of cases of tuberculoid leprosy. + = HB-Ag positive case; ● = HB-Ag negative case.

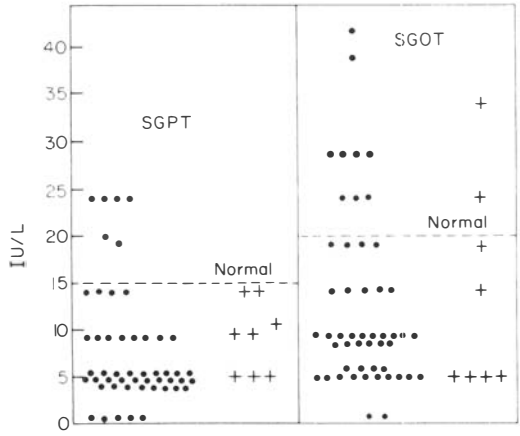

Fig.2. Scatter diagram showing SGPT and SGOT levels of cases of lepromatous leprosy. + = HB-Ag positive case; ● = HB-Ag negative case.

(Wooton, 1964). A reference to the table shows that the mean enzyme values of the 50 HB-Ag negative cases of tuberculoid leprosy are actually higher than the means for the seven cases which showed presence of antigen in the serum. The scatter diagram (Fig.1) shows that the range and values obtained are not essentially different. Moreover none of the HB-Ag positive cases had abnormal (raised) enzyme levels.

With lepromatous leprosy the results obtained were slightly different. The mean value of enzymes obtained in 50 cases of lepromatous leprosy not carrying HB-Ag were lower than those obtained with HB-Ag carriers having lepromatous leprosy. These slight differences, however, when analyzed by statistical methods proved to be of no significance (P=0.54 and 0.68). A glance at the scatter diagram (Fig.2) again brings out the essential similarity of the results in the two groups.

TABLE 1

SGPT and SGOT (International Units/L) in HB-Ag positive and negative patients with leprosy

	GROUP	No. of cases	SGPT Mean value	No. of cases with SGPT over 15 IU/L	SGOT Mean value	No. of cases with SGOT over 20 IU/L
(I)	Tuberculoid	57				
	HB-Ag negative	50	9.08	8	11.48	5
	HB-Ag positive	7	7.86	0	8.86	0
(II)	Lepromatous	58				
	HB-Ag negative	50	7.96	6	12.48	9
	HB-Ag positive	8	8.88	0	13.75	2

Discussion

The results for SGPT and SGOT, in general, are in keeping with the well documented observations that there are no serious derangements of liver function in leprosy (Shivde and Junnarkar, 1967). Progressive liver damage due to *Myco. leprae* is not known. Further, the results indicate that there is no difference in the enzyme levels in cases of leprosy with or without carriage of the hepatitis B virus. The inference that can be validly drawn is that the hepatitis B virus does not damage the hepatocyte to cause a rise in enzyme levels. Of the available tests these enzyme estimations are the most sensitive indicators of hepatic parenchymal damage. The interaction between the hepatitis B virus and the leprosy patient, therefore, appears to be that of symptomless carriage.

We still do not know for certain the outcome of symptomless HB-Ag carriage either in the leprosy patient or in normal individuals. The very fact that the hepatitis B virus is present in the serum in such large amounts as to be detected by relatively crude immunological methods indicates a considerable growth of the virus. The accepted site for this is the hepatocyte (Millman *et al*, 1969). Therefore disruption of some hepatocytes and hepatic damage is unquestionable. The point of interest is whether there is sufficient damage to disorganize normal liver regeneration so that a terminal condition like cirrhosis of the liver develops with the passage of years. A sequential follow-up study would finally decide this issue.

A lot of data is available in the literature regarding the condition of normal individuals carrying HB-Ag (Lous *et al.*, 1970; Singleton *et al.*, 1971; Lebacq, 1971; Ricci *et al.*, 1972). These studies prove that a variable number of HB-Ag carriers have hepatic injury, with the likelihood of development of cirrhosis of the liver.

Cirrhosis of the liver is not a common finding in patients with leprosy. Thus Kean and Childress (1942) noted cirrhosis in only seven of 103 patients studied at autopsy in Panama. Similarly Shivde and Junnarkar (1967), studying liver biopsies, found only five of 43 cases to have cirrhosis of the liver. In contrast, in a study of portal cirrhosis in patients without leprosy we have found as many as 34% to be associated with HB-Ag (Kelkar *et al.*, 1973*a*). This raises the question of the relationship of HB-Ag with cirrhosis of the liver in patients with leprosy. Because of the rarity of the combination, a study of a large series of such cases is not feasible. The indirect evidence of enzyme levels presented in the present study suggests that this is not a frequent happening.

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Lepr. Rev. (1974), **45**, 326-328

Reprinted Article

This paper, published in the *Journal of Archaeological Science*, 1974, **1**, 205-207, and reprinted here with permission, will be of interest to all our readers, as it provides strong evidence for the existence of leprosy in Britain as far back as the 4th century AD, and carries back by five centuries the first reliable record of leprosy in Northern Europe.

New Evidence for the Antiquity of Leprosy in Early Britain

RACHEL READER

Ancient Monuments Laboratory, Department of the Environment, 23 Savile Row, London, W1

Examination of skeletons excavated in Dorset has probably produced the earliest example of leprosy known in northern Europe. The site, Poundbury Camp, Dorchester, was excavated under the direction of C. J. S. Green for the Dorchester Excavation Committee from 1966 to 1973. It is a Romano-British cemetery, apparently Christian, and the leprous bones are dated by their archaeological context to the middle of the fourth century AD.

The specimen consists of the distal portions of right and left tibiae and fibulae, and the right and left feet. The right intermediate cuneiform is missing, but this may be a post-mortem loss. All parts of the skeleton above the mid-shaft of the tibiae and fibulae have been lost due to modern disturbance. It is therefore impossible to estimate the sex of the individual or its age, but the bones are certainly those of a mature adult.

The following pathological changes were noted.

Tibiae and Fibulae

The lateral and posterior aspects of the tibiae, and the medial and posterior aspects of the fibulae, show extensive pitting and furrowing, with small irregular osseous deposits. The effect is of chronic inflammatory periostitis. The right tibia shows a groove on the lateral aspect which crosses the longitudinal furrows, and may be vascular. These changes correspond with Møller-Christensen's (1961) descriptions of pathological tibial and fibular changes in leprosy.

Left Foot

This shows periostitic pitting and grooving on all the tarsals and on the distal articular facets of the first, second, third and fourth metatarsals. The fifth

metatarsal (arrowed, Fig.1) is almost completely resorbed to an irregularly-shaped fragment articulating with the proximal lateral facet of the fourth metatarsal. The medial cuneiform is ankylosed to the first metatarsal, with medial flexion of the proximal phalanx of the hallux. On radiographic examination, the distal articular end of the medial phalanx of the second metatarsal shows a small area of sub-periosteal destruction of pseudo-cyst type (arrowed, Fig.1).

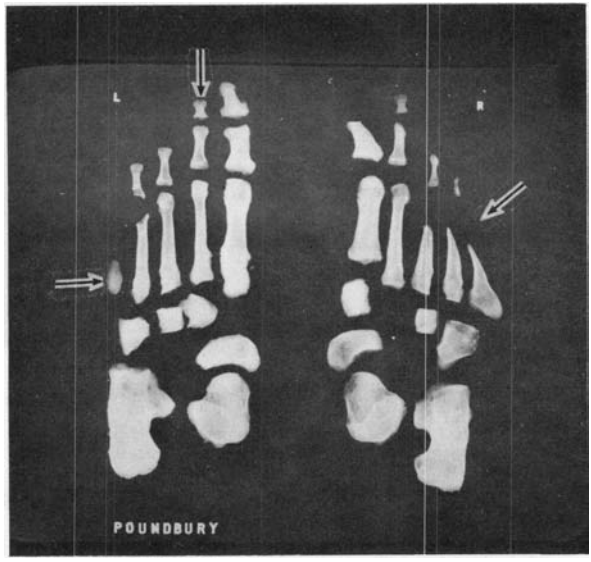

Fig.1. Radiograph of the feet of the Poundbury Roman leprosy skeleton.

Right Foot

This shows a similar generalised periostitis of the tarsals. The third, fourth and fifth metatarsals show marked resorption of the capitula, with extreme tapering of the shafts (arrowed, Fig.1). The proximal phalanges of the third and fourth metatarsals show distal disorganization and atrophy. The proximal phalanx of the hallux is laterally eroded and medially flexed.

These changes in the feet are closely parallel to those described by Møller-Christensen.

The tentative diagnosis of leprosy in the specimen from Poundbury Camp indicated by these changes has been confirmed by Dr W. H. Jopling, F.R.C.P., Consultant Leprologist to the Hospital for Tropical Diseases, London. The extensive nature of the bone changes suggests a type of leprosy similar to the modern lepromatous leprosy where the patient is incapable of producing a cell-mediated response to contain the spread of the bacillus (Jopling, 1974). Deformities of the hands and feet due to leprosy are frequently bilaterally symmetrical. This is not the case with the feet of the Poundbury Camp skeleton, which show a far more severe level of deformity to the right foot than to the left.

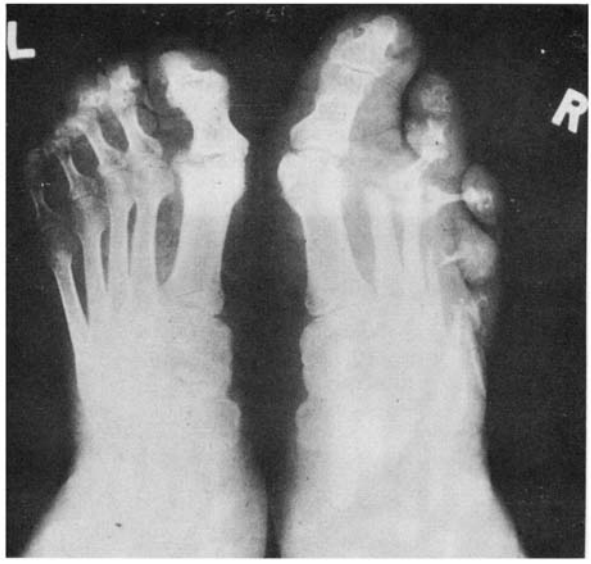

Fig.2. Comparable radiograph of the feet of a modern leprosy patient, showing similar pathological changes.

However, Fig.2 shows a very similar pattern of asymmetrical change in the feet of a present-day leprosy patient.

Despite the incomplete state of the skeleton from Poundbury Camp, there would seem little doubt that it represents a case of leprosy in Roman Britain. Work on the skeletal material from this site is not yet completed, and it is possible that further evidence of leprosy may emerge.

Acknowledgements

Figure 2 appears by courtesy of Dr Jopling, to whom I am extremely grateful for his examination of the specimen and of radiographs at very short notice, and for his advice and helpfulness. I should also like to thank Mr D. R. Brothwell and Miss Theya Molleson of the British Museum (Natural History) for advice and for providing radiographs. I am grateful to Mr J. Musty of the Ancient Monuments Laboratory, Department of the Environment, for arranging for the skeletal work on this site to be carried out, and for providing laboratory facilities.

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News and Notes

GOLDEN JUBILEE OF THE BRITISH LEPROSY RELIEF ASSOCIATION

G. FRANCIS HARRIS, M.C.

Director

Fifty years is a very short time in the known history of leprosy, yet it seems a long time when one looks back to the early 1920's, when Sir Leonard Rogers was a Major General in the Indian Medical Service, and Mr Frank Oldrieve the Secretary for India of the Mission to Lepers, now the Leprosy Mission. Sir Leonard Rogers had just completed the research at Calcutta on chaulmoogra which opened up a new era in leprosy treatment, giving hope for the first time that the disease might be eradicated. This vision, set against the tragic background of leprosy in India which both knew so well, brought both men together. At an historic meeting on 29 March 1923, the idea of a new, non-sectarian organization dedicated to the eradication of leprosy was mooted, and when Sir Frank Carter, also recently retired from India, offered to organize the financial side, the launching of the British Leprosy Relief Association (BELRA) followed in January 1924, under the patronage of the Prince of Wales.

The enthusiasm and great authority of Sir Leonard Rogers in particular gave importance and official standing to the Association from the outset, and Branches were formed in several countries administered by Britain. The Indian Branch, known for many years as the Hind Kusht Nivaran Sangh, has served independent India in a most outstanding way.

From the start, the main emphases of BELRA were on leprosy control, especially the promotion of treatment in the early stages, and in research in all its aspects. Throughout its history the Association has been served by a succession of distinguished leprologists in the role of Medical Secretary. The development of leprosy control work in territories administered by Britain overseas owed a great deal to visits made by the Medical Secretary of BELRA, often with official backing, and so able to stimulate interest and to concern at government level, while at the same time bringing encouragement and support to those actually engaged in leprosy control work. In several countries it was as a result of such visits, and the practical support of BELRA in both finance and personnel, that leprosy control work really began. The LEPRA leprosy eradication project in Malawi is a continuing example of the activity of BELRA in this sphere.

Certain other aspects of the Association's work stand out, and have stood the test of time. In 1928 *Leprosy Notes* was introduced, and developed into the *Leprosy Review* by 1931. At that time this was the only publication in the British Empire outside India which dealt exclusively with leprosy. Though by no means the only publication of its kind today it still is playing a most important role wherever the English language is understood.

1933 saw the foundation of LEPRA's overseas staff, following the Reverend Dr Clayton's visit to West Africa during the previous year. No one who has had any experience of leprosy control in Africa will doubt the wisdom and the foresight of Tubby Clayton in suggesting that TOC H and LEPRA should join forces to make available LEPRA workers for service overseas. A long succession of devoted workers followed, doctors, nurses, pharmacists, administrators, and accountants, and their contribution to the work has been very considerable.

The importance of early treatment had long been recognized, but it was not until 1937 that steps were taken to set up the Child Adoption Scheme, when the first 12 children became adopted. This Scheme provided the money needed to ensure the best treatment of children, thus preventing them from becoming disabled. With changes in treatment and the emphasis on domiciliary care the Scheme has been modified, and today more than 29,000 children receive their treatment at home as a result of grants made to organizations in India and Africa from the successor to the Child Adoption Scheme, the Children's Fund.

The fostering of research has always been a primary objective of LEPRA. There is no more outstanding example of this than the founding of the Research Unit at Uzuakoli hospital in 1947, destined to contribute so much towards leprosy therapy in succeeding years.

To be successful an Association has to adapt its methods to contemporary conditions. As will be seen, the overall policy decided upon when the Association was set up has largely stood the test of time, but the methods employed for fighting leprosy throughout a self-governing world have had to be modified. In 1964 BELRA became LEPRA. Now in this its Jubilee year, the optimism shown throughout the history of the Association is probably more surely based than it ever has been. LEPRA is currently becoming more and more involved with various aspects of leprosy research, since it is felt that the ultimate solution to the problem lies in finding quicker-acting drugs or a prophylactic. In view of the dramatic increases in knowledge over the past few years it is not unreasonable to assume that whilst during the first 50 years of the Association's existence the estimated number of cases of leprosy in the world has risen from 3,000,000 to 15,000,000, during the next 50 years there is every chance that the original object of the Association—the eradication of leprosy, will be achieved, not only from the British Empire, as it then was, but from the world.

PLANS FOR A COLONY OF ARMADILLOS IN ENGLAND

R. J. W. REES

Although the full impact of biomedical research in leprosy will be restricted until *Myco. leprae* can be cultured *in vitro*, important advances have been achieved since it was demonstrated that the leprosy bacillus could be grown in the mouse. In fact, from the time this was first achieved in 1960 using the "mouse footpad technique", experimental infections with *Myco. leprae* in the mouse and other small rodents have been exploited on an ever increasing scale. Growth of *Myco. leprae* in these animals has been applied wherever possible as a substitute for *in vitro* cultivation techniques used for other cultivable bacteria, and in addition the resulting experimental leprosy infections have been applied for studying the evolution and pathogenesis of the disease.

The direct and indirect application of these animal infections have provided, for the first time, the means whereby *Myco. leprae* can be studied in the laboratory, and have already encouraged workers in many other disciplines to undertake leprosy research. In the period of only 14 years since this animal infection was developed, it has contributed significantly to our knowledge of the pharmacodynamics of dapsone, the introduction of acedapsone and rifampicin for the treatment of leprosy, proof of the existence of dapsone resistant strains of *Myco. leprae*, new knowledge of the pathogenesis of leprosy neuritis, and the role of cell-mediated immunity in determining the "resistance and susceptibility" of the host. The latter findings were based on the fact that multiplication of *Myco. leprae* in the "normal" mouse was limited and reached a plateau six months after inoculation whereas mice made immunologically deficient (T-cell deficient) by thymectomy followed by total body irradiation, supported the continuous growth of *Myco. leprae* more or less throughout their 2-year life-span. Such mice replicated the bacterial and histopathological picture seen in patients with lepromatous type leprosy.

Thus, in the period 1960-1971 infections with *Myco. leprae* in the mouse and to a limited extent in other rodents, dominated the advances in leprosy research, mainly with a limited infection but also in an enhanced infection which could be artificially produced in the mouse by obliterating its cell-mediated immunity. In 1971 another and most important animal model was presented to the world by Kirchheimer and Storrs, who showed that the nine-banded armadillo (*Dasypus novemcinctus,* Linn.) could without any prior manipulation of its cell-mediated immunity develop a progressive lepromatous-like infection when inoculated with *Myco. leprae*. These two workers were based in Louisiana where this species of armadillo is commonly found. It is a large mammal weighing 3-5 kg and has a life-span of approximately 15 years, compared with a 25 g mouse with a life-span of only 2 years. Thus, the armadillo has tremendously important potentials for leprosy research. In particular the fact that at least a proportion of these animals develop, without any sophisticated immunological manipulation, a spontaneous heavy infection when inoculated with *Myco. leprae*, provides, for the first time, a laboratory source of *Myco. leprae* on a massive scale. Thus, while the readily available mouse substitutes conveniently for routine *in vitro* cultivation of *Myco. leprae,* the armadillo substitutes for the large-scale *in vitro* cultivation of *Myco. leprae*. Therefore, these two animal models should go a very long way towards enabling nearly all aspects of basic and applied research on *Myco. leprae* to be achieved without actually culturing the causative organism *in vitro*. Recent intensive studies on the armadillo in Louisiana have shown that the animal can be adapted to laboratory conditions and that a relatively high proportion of animals inoculated (probably up to 60%) develop progressive infection when inoculated with strains of *Myco. leprae*.

In June this year I visited Dr E. Storrs at the Gulf South Research Institute, New Iberia, Louisiana, to learn the techniques of husbandry and to arrange for her to despatch to England 20 laboratory adapted nine-banded armadillos. With her collaboration these animals are expected to arrive by air in England some time in October. Allowing about a month for them to acclimatize to our local conditions they will then be inoculated with *Myco. leprae* in November. From recent knowledge we can anticipate up to 12 of the animals developing in about 18 months a progressive infection. This, at least, is the anticipated rate of infection from experience with these animals in Louisiana. The importance of this

exercise will be to establish first of all that these infections can be reproduced in England, and if they can then in about 18 months a large supply of *Myco. leprae* will be available for research workers in this country. Biopsies of tissues will be taken from the armadillos at intervals following infection in order to determine their progress. Once such biopsies are shown to be positive, further consignments of laboratory adapted armadillos will be imported in order to maintain a continuous colony of leprosy infected armadillos for long-term research in the United Kingdom.

A major part of the financial support for this programme will be provided by LEPRA.

LEPRA MEDICAL ADVISORY BOARD

The Executive Committee of LEPRA when considering the complexity of leprosy, has decided that, in order to have the best advice available on all its aspects, the former Medical Committee should be replaced by a Medical Advisory Board (M.A.B.). Members of the M.A.B. would be appointed for three years initially with the possibility of further appointments provided they are still engaged in the medical discipline they were originally appointed to cover.

The following members have accepted appointment:

1.	Clinical	– Dr W. H. Jopling
2.	Clinical Research	– Dr C. McDougall
3.	Epidemiology	– Dr T. Meade
4.	Editor of *Leprosy Review*	– Dr T. F. Davey*
5.	Field Work	– Dr D. Molesworth
6.	Histopathology	– Dr D. Harmen
7.	Immunology	– Prof. J. L. Turk
8.	Medical Education	– Dr C. McDougall
9.	Microbiology	– Dr R. J. W. Rees*
10.	Neurology	– Prof. G. Weddell
11.	Pathology	– Dr D. S. Ridley*
12.	Pharmacology	– Dr G. Ellard*

(* Members of the Editorial Board of *Leprosy Review*.)

NEW LEPRA FILM: *LEPROSY*

LEPRA announces the release this autumn of a new film for the general public entitled *Leprosy*, and designed to present the facts about leprosy in their present day setting. Much care and skill have gone into the making of this film, and Sir Harold Himsworth, K.C.B., F.R.S., M.D., F.R.C.P., a Vice-President of LEPRA has contributed the following background to the film.

Perhaps no other ill that affects man has excited such fear and repulsion as leprosy. It is not surprising that this should be so, for the results of the disease are dreadful, the disfigurement it produces appalling, it is contagious and no respecter of persons, and until comparatively recently, all men's efforts to arrest its insidious progress were largely unavailing. Is it any wonder then that over the ages a mythology accumulated round leprosy which has coloured the whole attitude of

human societies towards its unfortunate victims and inclined them to avert their gaze from the problem it poses?

But times are changing. In the 1940's the discovery of sulphone treatment was an outstanding advance, both in the treatment of active leprosy and in reducing the period in which sufferers from leprosy were capable of infecting others. The gains thus made have been considerable. But, as every physician knows, the only way to conquer chronic infectious disease is to prevent it. The crucial steps to this end are to reproduce the disease in experimental animals and to cultivate the organism that causes it outside the body. Only thus is it possible to accelerate the production of drugs for treatment and to entertain the possibility of a vaccine for prevention. In the case of tuberculosis, the disease most closely related to leprosy, we found out how to do these things many years ago, and the fact that we are now within sight of getting the measure of this condition can largely be attributed to our having done so. But, until very recently, leprosy defeated all our efforts to do likewise. Now, however, we have discovered how to produce the disease in animals and, although we are still unable to grow the causative organism, it is clear that the day when we can hope to attack leprosy at its source, rather than simply defend ourselves against its manifestations, is now dawning.

That is the theme of the new chapter that is now opening on our field. Clearly, as LEPRA has appreciated, it points to an intensified research effort. But its implications go beyond this.

Leprosy has now been brought into the category of diseases that are yielding to scientific research. This should do much to orient human societies to regard it as a disease like any other and, as such, something with which it is their duty to deal. There is much that can be done at present. Further, even if we are successful and find a way to prevent leprosy and obtain drugs that will decisively and quickly cure it, there will still be an enormous legacy of casualties from a previous era whose lot has to be ameliorated. That era is today and the casualties are occurring daily. Given a reasonable hope of ultimate success, men are prepared to make greater efforts to develop what they have. If they are to do this, however, they must first be convinced that their efforts will not be wasted. This is where a body like LEPRA has an invaluable part to play. It is for this reason that we should be grateful to the Executive Committee for commissioning the production of that excellent film *Leprosy*. Nobody I think can see this without realizing, not only the promise of the future, but also what it is possible to achieve in the present. And having seen this, it will be difficult for them to pass by.

CLASSIFICATION OF LEPROSY

A set of transparencies covering the clinical and histological spectrum of leprosy has been prepared by Drs W. H. Jopling and D. S. Ridley on behalf of LEPRA and is available on request without charge. The set of 10 clinical and 14 histological transparencies, accompanied by legends and information, is suitable for teaching purposes. Apply to the Secretary, LEPRA, 50 Fitzroy Street, London, W1P 6AL.

Lepr. Rev. (1974), **45**, 334-341

Leprosy and the Community

LEPRA–LEPROSY CONTROL PROGRAMME, MALAWI ANNUAL REPORT 1973

1973 was the eighth year of the comprehensive leprosy control project organized by LEPRA in Malawi with Dr B. D. Molesworth as Director. Dr Molesworth's annual report for 1973 includes the following.

GENERAL

The whole approach to leprosy work in Malawi has undergone a radical change and various projects which had been under discussion for some time became realized. With the visit of Mr F. Harris, Director, LEPRA London, in March, all facets of the work were discussed and in the outcome virtually the whole country can be brought under close coverage.

In general terms:

(i) The Northern region work will become the responsibility of LEPRA and to this end a group of houses were purchased from Messrs W. & C. French Ltd, who were relinquishing them on completion of their contract. These are at Chilumba, on the Lake shore, 40 miles south of Karonga. This will make an ideal headquarters for the work which, in the first phase, will be in the Chitipa, Karonga, Chilumba and Rumphi districts. Dr Gjalt is in charge and moved there in October.

(ii) The Central Region is the site of a new scheme for the outpatient treatment of both leprosy and tuberculosis. This work is being undertaken with the co-operation of D.A.H.W., The German Leprosy Relief Association, and is financed by them with the assistance of the Order of Malta, and LEPRA being responsible for the field work. This is a very important advance and, if proved successful, could completely alter the approach to tuberculosis treatment in the country. Dr Warndorff is in charge and began work there in July. At present the project is confined to the districts of Lilongwe (the new Capital) and Mchinji, but will expand to the rest of the Central Region. The Leprosarium at Kochirira will provide ward accommodation and will be the base for one mobile unit. At Mua the Mission Leprosarium has begun mobile work in the surrounding area and the wards are to be improved while the "residential" accommodation is reduced and finally discontinued. Mua is on the railway and is now connected with a good bus service to Balaka.

(iii) South of these areas and north of the original LEPRA project area, the country is divided north to south by the Lakes Malawi, Malombe, and the Shire River. The new leprosy hospital at Balaka, built by the Daughters of Wisdom, is now operational and Dr Krenzien is in charge. One outpatient circuit is already in action and a second is planned which between them will cover the land to the west of the divide, the work based on Likwenu and

started and run by Mr Walters, will continue, and will expand northwards to include all Malawi territory to the east of the Lake/River division. The wards at Likwenu will be retained while the housing accommodation will be discontinued, and cases requiring surgery or more specialized treatment will be transferred to Balaka. Thus, Balaka will be seen to be at the hub of road and rail communication and forms the centre of this large and densely populated area of work.

(iv) To the south again comes our original project area now reaching the stage of integration with existing health facilities but over which we shall retain surveillance.

(v) Finally, the very difficult area of the Lower River (Shire) which has become the care of the Seventh Day Adventists, using their leprosy wards at Malamulo, and setting up outpatient work in the valley.

All this work will be coordinated by LEPRA working in close collaboration with the Ministry of Health.

PROJECT AREA

As the case load has diminished, it has been possible to modify the original circuits with push bicycles being used (three replacing one Land Rover), and in charge of three cycles is a Medical Assistant using a motorcycle. This has proved successful and the more personal approach has shown in the attendance figures. The work of reviewing and, where possible, discharging, has continued.

NORTHERN REGION

Since Dr Gjalt only moved to his headquarters at the end of October, the work has been largely one of settling in and becoming acquainted with the area and the people. This has been mostly confined to the coastal area from Chilumba to Karonga. Staff and equipment have been gradually built up and the radio link has proved of great value.

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CENTRAL REGION

This part of the work is now six months old. Housing and temporary office accommodation were obtained and vehicles arrived from U.K. Work has begun on the new Centre. Progress has been made in the localizing of both leprosy and tuberculosis patients, somewhat hampered by hold-up in the secondment of staff due to the outbreak of cholera requiring all available health personnel. Mobile treatment runs are being planned which include both leprosy and tuberculosis patients. The role of Mua Leprosarium has already been mentioned.

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BALAKA

With the arrival of Dr Krenzien in June, the outpatient work is on a firmer basis with known "cases" being reviewed and new admitted. Hitherto these had not been seen by a doctor. Half the ward accommodation was given over to cholera cases owing to an explosive outbreak in the area.

Vehicles are available and a second circuit is planned westward to the border.

LIKWENU

Whilst Mr Walter has continued to run the leprosarium and the outpatient

circuit attached, preliminary planning has been undertaken for the extension of the work northwards. Money was made available for capital expenditure from a legacy in America and half the recurrent costs have been promised by the American Leprosy Mission with LEPRA underwriting the remainder. Mr Walter is due to retire early in 1974 and Mr Buller will take over his work and that of the extension.

LOWER SHIRE

This has proved a problem area. The preliminary work was encouraging and then lapsed owing to the attempt to cover too much ground to start with. Then in October cholera broke out making movement very difficult. At this time, Mr Howson went on leave. Fortunately, Mr Knutsen, a final year medical student from Oregon, was able to give four months service during which two runs were worked out and a great deal of village work done. This has proved a most valuable start and the methods can now be extended.

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STATISTICAL REPORT

Total cases registered	13,027
Still on treatment register	6,246
Total discharged by end of 1973	2,574

Patients charted

1973	1972	1971	1970	1969	1968	1967	1965 & 1966
536 (4%)	635 (5%)	806 (6.5%)	1022 (8%)	1243 (10%)	2335 (18.5%)	2918 (23%)	3532 (29%)

Patients under treatment by sex and class

Lepromatous		Non-lepromatous		Total
male	female	male	female	
1251(20%)	704(11%)	1741(28%)	2550(41%)	6246

New cases 1973 by sex and class

Lepromatous		Non-lepromatous		
male	female	male	female	
101(21%)	48(10%)	157(32%)	176(37%)	482

(54 cases previous treated but unregistered brought this total to 536.)

The trend in 1972 has continued. New cases are now only 4% of the total. Patients under treatment have fallen in numbers as a result of discharges, mostly of tuberculoid cases. This has led to an increase in the lepromatous rate and the male rate.

Participation in two general hospital skin clinics has led to the discovery of 197 cases of leprosy.

SCHIEFFELIN LEPROSY RESEARCH SANITORIUM, KARIGIRI, S. INDIA ANNUAL REPORT 1972-73

The Schieffelin Leprosy Research Sanitorium, for the past 19 years the principal research centre of the Leprosy Mission, is one of the leading leprosy research and teaching institutions in India. Its annual report for 1972-73 lists 29 papers

contributed to scientific journals during the year. It is not surprising that at the centre where Paul Brand undertook some of his historic work, there should be a continuing emphasis on the surgical aspects of leprosy, both reconstructive and preventive. Under the leadership of Dr D. A. Ranney, 266 orthopaedic and plastic operations were carried out, while the Department of Physiotherapy and the Orthopaedic and shoe workshops both continued their large scale and varied activities. On the medical and laboratory side, Professor Job's relationship with the hospital has continued, and every department has indeed set the highest standards in a research orientated hospital.

The extensive leprosy control project in Gudiyatham Taluk, started in 1962, is of particular interest, in that a population of over 400,000 is being kept under continuous surveillance for leprosy in a carefully planned project. In 1970, the estimated leprosy prevalence was 26 per thousand. The first survey of the population was completed in 1966. New cases detected since then are as follows.

Year	No. of new cases	Below 15 years of age	Lepromatous rate (%)
1967	546	37%	11.7
1968	440	38%	10
1969	400	38%	14
1970	963	43%	12
1971	923	38%	11
1972	828	30%	8.6

These figures exemplify the problems of leprosy control in India.

Teaching has been undertaken by all departments, and embraced doctors, physiotherapists, occupational therapists and health workers from several countries.

During recent years the hospital has owed much to the wise and dedicated leadership of Dr P. V. Kurian, and we offer good wishes both to him in his retirement and to Dr Ernest Fritschi who succeeds him.

Field Workers' Forum

TREATMENT OF REACTIONS IN LEPROSY

M. F. R. WATERS

Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, Selangor, Malaysia.

Reactions comprise the most serious group of medical complications occurring during the course of treatment of leprosy. Hitherto, their classification has been controversial, the mechanisms of the different types unknown and treatment largely empirical. They have frequently caused prolonged morbidity and hospitalization of leprosy patients, and have often resulted in unsightly scarring and sometimes permanent deformity.

*Reprinted from Proceedings of the 6th Singapore-Malaysia Congress of Medicine, 1971.

Classification and Differential Diagnosis

Collaborative work by the Leprosy Research Unit, Sungei Buloh, initiated in 1967 and still continuing, has shown that the majority of reactions may be classified into two aetiological groups (Waters *et al.*, 1971). The principal points of differentiation are listed in Table 1.

TABLE 1

Comparison between the two main groups of "reactions" occurring in leprosy

	Erythema nodosum leprosum	Lepra reaction
Type of leprosy in which reaction occurs	Lepromatous and small numbers of borderline lepromatous	Whole of leprosy spectrum except polar lepromatous and polar tuberculoid
Relationship to treatment	Treated patients greatly exceed untreated	Untreated ("Downgrading Reaction") patients. Treated ("Reversal Reaction") patients
Manifestations	Crops of painful papules developing in a few hours and lasting a few days. Successive crops may occur over many months or years	Leprosy lesions themselves gradually become swollen and erythematous (new lesions may also appear); reaction lasts for weeks or months
Complications	Neuritis, iritis, orchitis, lymphadenopathy, arthritis, proteinuria	Ulceration of skin, neuritis
Histology	Vasculitis, polymorph infiltrate, fragmented leprosy bacilli	No extraneous infiltrate
Change in leprosy classification	Does not occur	Untreated patients–shift toward lepromatous. Treated patients–shift toward tuberculoid
Aetiology	Immune complex disease	Change in cell medicated immunity against *Myco. leprae*
Suppressed by	Steroids Thalidomide Clofazimine	Steroids Clofazimine

The first group, usually known as *erythema nodosum leprosum* (ENL, lepromatous lepra reaction), occurs in more than 50% of lepromatous and small numbers of borderline- lepromatous patients, principally during treatment. It consists of episodic eruptions of painful red papules, usually accompanied by fever and malaise, and neuritis, orchitis, iritis, lymphedanitis, arthritis and proteinuria may also occur. Histologically there is polymorph infiltrate and vasculitis. We have produced good evidence that ENL is due to the formation of

immune complexes consisting of mycobacterial antigen, immunoglobulin and complement (Wemambu *et al.*, 1969; Waters *et al.*, 1971). The second group, usually named "Lepra Reactions", occur in all types of leprosy save polar lepromatous (LL) and polar tuberculoid (TT). Here the leprous skin lesions themselves are inflamed for many weeks or months; clinically and histologically they are consistent with the type of leprosy the patient is suffering from or developing, and there is no extraneous inflammatory infiltrate. Ulceration of the skin and neuritis are not uncommon complications. In general, the end result of such reactions is a shift in leprosy classification; an untreated patient who develops a lepra reaction becomes more lepromatous ("Downgrading Reaction", Ridley, 1969); whereas treated patients become more tuberculoid ("Reversal Reaction"). There is substantial evidence from our lymphnode studies (Turk and Waters, 1968, 1971; Waters *et al.*, 1971) and from experimental leprosy (Rees and Weddell, 1968) that such reactions are associated with changes in cell mediated immunity against *Mycobacterium leprae.*

Treatment of Severe Reactions

The following recommendations summarize 12 years experience and six controlled clinical trials in reactions performed at the Leprosy Research Unit.

(1) ENL

It is traditional to reduce dosage or to stop completely treatment with dapsone (WHO Technical Report, *Leprosy,* 1966), to give anti-inflammatory drugs and stibophen; and in very severe ENL to give steroids, although the risk of steroid toxicity is great.

We disagree completely with stopping effective anti-leprosy treatment because: (1) We find no evidence that the incidence and severity of ENL is less on low dosage as compared with high dosage dapsone (Waters, 1968). (2) In a double blind study in established ENL, restarting dapsone after a period off anti-leprosy treatment did not result in an immediate worsening of the reaction (Pearson and Helmy, 1973). (3) Even in the most severe prolonged ENL, the reaction always eventually dies away, perhaps after several years, provided that effective anti-leprosy treatment is continued. (4) Prolonged stoppage of dapsone allows the small numbers of persisting viable leprosy bacilli present to multiply, increasing the patient's load of mycobacterial antigen and thereby increasing the total duration of the reaction.

Therefore we continue dapsone in full dosage throughout ENL. If the ENL cannot be adequately controlled by anti-inflammatory drugs and stibophen (i.e. if there is prolonged fever and malaise or if any complications such as iritis or neuritis develop) then there are three alternative regimens.

(A) Dapsone plus prednisolone. Steroids very rapidly control ENL, they can be given to nearly all patients, but because they are usually required in high dosage (e.g. 20-60 mg prednisolone daily, and one patient required 160 mg!) for many months or years they frequently result in significant steroid toxicity, and we have seen several patients with collapsed vertebrae due to steroid osteoporosis.

(B) Dapsone plus thalidomide. Thalidomide quickly and effectively controls nearly all cases of ENL (Sheskin, 1965; Pearson and Vedagiri 1969; Waters, 1971). The drug has immunosuppressive properties, although its exact mode of action is unknown, and there is no dose for dose relationship with prednisolone.

The one toxic effect we have seen is occasional mild allergic dermatitis (easily controlled with anti-histamines); drowsiness is largely avoided by giving the main dose of the day at 4 or 6 p.m. We have no evidence of neurotoxicity, and indeed thalidomide seems particularly valuable in ENL neuritis (Sheskin *et al.*, 1969). It is frustrating that such a generally safe and effective drug, which would enable many ENL patients to return home and to work, cannot because of its teratogenic properties, be given to premenopausal females, and should only be prescribed under most carefully supervised conditions. Initial dosage is 300-400 mg daily, usually reducing to a maintenance dose of 50-200 mg daily.

(C) Clofazimine (B663). This rimino-phenazine derivative has both anti-mycobacterial and anti-inflammatory properties (Vischer, 1969). Therefore it can be given by itself in the treatment of ENL. Although it causes occasional mild diarrhoea it appears to be a safer drug than either prednisolone or thalidomide, is applicable to all patients with ENL, and is especially valuable for out-patient treatment. It has two disadvantages;

(a) it causes a deep red-brown discolouration of the skin, unpopular in light-skinned patients;
(b) it is slower acting than the other two drugs, and may not adequately control the most severe cases of ENL.

Pettit (1967) has shown that 100 mg daily was insufficient dosage for his patients, although Helmy (1971) has found good response with 300 mg daily in a less severe group of patients. The dose should not exceed 400-500 mg daily (Working Party, 1969) and if this fails to give adequate control then additional treatment with small doses of either prednisolone, or (in male patients) thalidomide should be given.

In summary; the treatment of ENL depends on the individual patient's circumstance, but the reaction may usually be well controlled, and many patients are now able to return to work on treatment.

(2) LEPRA REACTION

Adequate treatment is important, as patients may rapidly develop ulceration of the skin, leading to a bad cosmetic result, and neuritis producing temporary or permanent nerve damage.

Effective anti-leprosy treatment should be initiated (in "downgrading reactions") or continued (in "reversal reactions"). If anti-inflammatory drugs and stibophen prove inadequate, the great majority of reactions may be quickly and easily controlled with prednisolone in relatively low dosage, e.g. initial dose of 20-30 mg daily, which may usually be reduced to 10-15 mg daily after a few days. Steroids may have to be continued for several months, but toxicity is uncommon.

Clofazimine is also effective in most cases of lepra reactions, although it acts less rapidly than steroids, and may be given as sole treatment or else substituted gradually for prednisolone once initial control has been achieved. But thalidomide has no significant effect, and should never be used in this group of reactions.

UNCERTAINTIES IN TREATMENT

In ENL it is traditional to give the minimum dose of the chosen drug just sufficient to suppress the reaction. However intermittent neuritis may occur, and very rarely renal damage and/or amyloid disease. The possibility that either mono or dual therapy (i.e. clofazimine and/or thalidomide and/or prednisolone) in

dosage above the minimal reaction-suppressive dose may give better long term results is being considered.

In lepra reaction, progressive nerve damage may rarely develop despite treatment with steroids and/or clofazimine in dosage which adequately suppresses all signs of reaction in the skin. This is being investigated.

Nevertheless with the greatly increased understanding of reactions in leprosy obtained within the last three years, both the immediate comfort and the long term prognosis of the reaction patient is very greatly improved.

Summary

From experience gained in the Leprosy Research Unit, Sungei Buloh, over the last 12 years, and from six controlled drug trials, schemes of treatment of the two main groups of reactions in leprosy are described. The importance of continuing effective anti-leprosy treatment in *erythema nodosum leprosum* (ENL) is emphasized. The relative value of steroids, thalidomide and clofazimine in ENL, and of steroids and clofazimine in lepra reactions is discussed.

Acknowledgements

The Leprosy Research Unit, National Leprosy Control Centre, is administered jointly by the Malaysian Ministry of Health and the British Medical Research Council. I am grateful to the Academy of Medicine, Singapore, for permission to reprint this communication.

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Addendum

In a series of recent papers, Godal and his colleagues have produced, good evidence that reactions in polar tuberculoid leprosy, whether treated or untreated, are due to the development of very adequate cell mediated immunity. Therefore the treatment of such reactions is similar to that described for "Reversal Lepra Reactions".

Field workers without indirect access to clofazimine and thalidomide are under a great disadvantage in treating severe ENL. It would appear highly desirable for regional centres to be set up in leprosy endemic areas, possessing adequate supplies of these drugs, to which patients suffering from severe ENL could be referred.

[a] See Helmy, H. S., Pearson, J. M. H. and Waters, M. F. R. (1971). *Lepr. Rev.* **42**, 167.

Lepr. Rev. (1974), **45**, 342-344

Letters to the Editor

Rapid Identification Tests for *Mycobacterium leprae*: A Clarification

I reported earlier a method for "A Rapid Identification Test for *Mycobacterium leprae*" (Prabhakaran, 1973). The method involved incubating a drop of the bacterial suspension with a drop of dopa (3,4-dihydroxyphenylalanine) solution on a slide. Of over two dozen species of mycobacteria tested in our earlier studies, only *Myco. leprae* was found to convert dopa to a pigmented product *in vitro*. Since the publication of the report, inquiries have been received asking for more details of the procedure, especially regarding the amount of bacilli used. In our experiments, the bacterial suspensions usually contain 1.0×10^9 organisms/ml. Sometimes, suspensions with 1.0×10^{10} bacilli are also used. It is important that, when different species of mycobacteria are tested, the number of organisms in all the suspensions is kept the same, so that photomicrographs taken will show the distinction between the enzymic and the non-enzymic oxidation of dopa. We enumerate the bacilli by the Hanks-Lechat-Chatterjee method, modified by Kirchheimer. It is essential that the spots on the slides are of approximately the same diameter and that they are not allowed to dry up. The bacterial suspensions we use are free of visible tissue debris and have occasionally been treated with alkali, ether or acetone. The success of the method depends on the condition of the bacilli as well. We have shown that bacilli separated from tissues of armadillos infected with *Myco. leprae* oxidize D-dopa to melanin. When the organisms were obtained from autopsy material, the dopa oxidase activity was rather low and inconsistent, indicating that the enzyme is labile. If the animal had been dead for a long time, the bacteria contained very low levels of the enzyme. However, the organisms from biopsy material gave good results (Fig. 1). The biopsies were fresh or frozen.

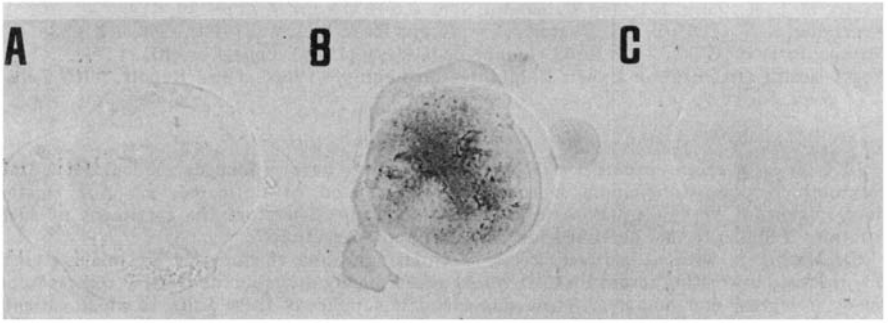

Fig. 1. A. Bacilli (Armadillo). B. Bacilli + D – Dopa. C. D – Dopa.

It has been reported (Convit and Pinardi, 1972) that when smears of *Myco. leprae* or tissue sections containing *Myco. leprae* are treated for 2 h with pyridine at room temperature, the bacilli lose their acid-fast staining property; several other mycobacteria tested retained their ability to stain with carbolfuchsin. The results were interpreted to suggest that in *Myco. leprae,* pyridine removes some component essential for Ziehl-Neelsen staining. This might well be so. It is also likely that the property is correlated with the *o*-diphenoloxidase of *Myco. leprae.* This enzyme activity has not been detected in other mycobacteria. The *o*-diphenoloxidase of the leprosy bacillus is non-specific and it oxidizes, besides dopa, a variety of other substrates. One of these substrates is mimosine. This compound has a pyridine ring instead of the benzene ring, although the alanine side chains are the same in both dopa and mimosine (Prabhakaran *et al.,* 1972). Mammalian and plant "tyrosinases" were inhibited by mimosine. Our observations suggest that *Myco. leprae* can bind pyridine, while other mycobacteria do not. The phenol in carbol fuchsin probably enables the dye to penetrate the bacterial cell. Since *Myco. leprae* can bind pyridine, pretreatment with pyridine would interfere with penetration of the dye into the leprosy organisms, and as such the bacilli fail to stain with carbol-fuchsin.

K. PRABHAKARAN

USPHS Hospital
Carville, Louisiana, U.S.A.

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The Terminological Question

In reference to the terminological question, I was pleased to read (*Lepr. Rev.* (1973) **44**, 94) that Dr Skinsnes considers my point about the situation in Brazil being different from Hawaii in many respects, "perhaps well taken." Unfortunately, it has never been easy for minorities to have their opinions accepted, so that I was not surprised when he added that "indeed, this is one reason that one wonders at the effort to change world-wide practice in order to achieve a social and cultural change in Brazil"—to which I must add a much needed prophylactical progress as well.

Our future would perhaps appear less gloomy if we could think of "leprosy" ("lepra", etc.) not quite as a "world-wide practice", but only as a word with ancient pejorative overtones in the English and Romance languages, which could be abandoned with a bit of goodwill. Also, when it is realised that Brazil is far from being the only victim of the complex "Leprosy, the Word, the Disease," (*Lepr. Rev.* (1972) **43**, 96) other countries might eventually join in our fight as well.

Studies conducted in the U.S. by Rolston and Chesteen (which concluded that "leprosy" is "the most negative of all medical terms") and at Carville, U.S., by Pearson, as well as by Mangiaterra in Argentina, should convince Dr Skinsnes that the movement to eradicate the term "leprosy" ought not to be brushed aside as pure "emotionalism". This is further emphasized by the fact that the new terminology has been recommended by three Brazilian congresses, accepted by the Brazilian *Nomenclatura Dermatologica* (Rabello) and *Nomina Dermatologica* (Gaspar and Gaspar), put into practice by six state public health services and about 40 medical schools in 12 states.

Denying that he was a "determined opponent" of the term "Hansen's disease" in Hawaii, Dr Skinsnes states that "Dr Rotberg clearly did not make a reasonable 'search of the literature' as he implies". Clarifying my controversial point 8, what I meant was that a determined opposition did exist *in Hawaii,* well known to all who keep up with the literature. I cited Dr Skinsnes because I thought of him as a good representative of that opposition: in three of the five articles of his series "Leprosy in Society" (*Lepr. Rev.* (1964) **35**, 175–(1968) **39**, 222–*Int. J. Lepr.* (1970) **38**, 294) the ancient movement against the appelation "leprosy" is criticized. The pamphlet he sent to me was just one example, but it did not actually provide me with any new information on this matter, as it practically repeated what I had read years ago in *Lepr. Rev.* (1964) **35**, 175. Furthermore, his antagonism to a new terminology continues even after the conclusion of the activities of the Hawaiian Citizen's Committee: Dr Skinsnes' letter to the *Far East Medical Journal* ((1971) **9**,307) of south-east Asia, opposing the highly favourable opinion of Dr Mallac, of Geneva, in regard to the Brazilian changes (*Far East Med. J.* (1971) **7**, 108), contributed to my appraisal of his position. According to Dr Skinsnes I overestimated his role, but the essence of point 8 remains: a determined opposition in Hawaii, in contrast with the present wide acceptance of the new terminology "hanseniasis" in Brazil, might have been one of the causes of the non-success of the Hawaiian experiment with "Hansen's disease".

In response to an appeal by 117 signatories from 15 countries, the Council of the International Leprosy Association decided at Bergen (1973) that each country may adopt their preferred terminology. This is not going to be of great value to us as long as the powerful English and French literature conserves the ancient word, but is at least an acknowledgment of the inconvenience of the term "leprosy" in some areas. We are hoping that this new policy of the I.L.A. will be accepted by its members, and we will be counting on Dr Skinsnes' prestige and influence to help us in this respect.

A. ROTBERG

Instituto de Saúde,
C. Postal 8027,
01000–Sao Paulo SP,
Brazil.

Book Review

Paediatric Priorities in the Developing World by David Morley
London, Butterworths, £1.25.

This book is dedicated to all those striving for the underprivileged children in our world. Many of these are exposed to infection with *Myco. leprae,* and not a few have clinical leprosy. This book is of importance to leprosy field workers, not only because child health constantly impinges on their work, but also because in areas of serious leprosy prejudice an approach through child care may be the most valuable means of winning the confidence and cooperation of the people. As Professor Wolff writes in his foreword, this book will be deeply appreciated by all doctors working with children in the developing world. It is a companion volume to Maurice King's *Medical Care in Developing Countries,* applying to paediatrics the principles and practical concerns of that historic book. Leprosy is given its proper place in the spectrum of endemic disease, and the book is packed with sound practical advice for all field workers concerned with child health. At a net price of £1.25 the paperback is of outstanding value.

T. F. DAVEY

Abstracts

It is regretted that extreme pressure on space in Volume 45 has necessitated the deferment of Abstracts from Journals to the next issue of the *Review.*

Obituary

As this issue of the *Leprosy Review* goes to press, news has been received of the death of Dr Ernest Muir, former editor of this journal, and a leprologist of great distinction and international renown. A tribute to his memory will appear in the next issue.

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