LEPROSY REVIEW

Volume 53, Number 4, December 1982

Published Quarterly for the
British Leprosy Relief Association

ISSN 0305-7518

Lepr Rev (1982) **53**, 243–247

Retirement of Dr R J W Rees

In September this year, Dr R J W Rees retired from his position as Head of the Laboratory for Leprosy and Mycobacterial Research at the National Institute for Medical Research (NIMR), Mill Hill, London. He will be succeeded by Dr J Colston at the NIMR, but will retain his long-standing association with LEPRA as Chairman of its Medical Advisory Board and Vice-Chairman of the Editorial Board of this Journal.

Difficult though it will be to pay realistic tribute to the extraordinarily high quality of Dick Rees's contribution to the subject of leprosy over several decades, we shall nevertheless be making an attempt to do this in a future number of *Leprosy Review*. Around mid-1983, it is hoped to devote an issue of the Journal to articles by leading authorities on the most important aspects of leprosy, which will summarize the present state of knowledge and reflect his outstanding participation over a long period of time. Meanwhile, to mark his formal retirement from Mill Hill, we print the following personal tributes.

From 'Close colleagues in London'

In the early fifties Dr James Doull, then the distinguished head of the Leonard Wood Memorial Foundation, suggested to a small informal meeting in London that it was time that leprosy research emerged from the descriptive stage into a subject more susceptible to scientific discipline and more attractive to medical scientists. A few years later the young Dick Rees, who was initially taken on to the staff of the NIMR to assist Dr Philip D'Arcy Hart in laboratory tuberculosis research, made his first successful venture into leprosy research by adopting a suggestion of Dr John Hanks that he take up tissue culture to try to grow the then uncultivated 'rat leprosy bacillus' (*Mycobacterium lepraemurium*). With Garbutt, Wong and Barr (1958–62) he demonstrated unequivocal growth of this organism in an established line of cells (rat fibroblasts). Since then he has exercised enormous and world-wide influence in transforming the study of leprosy into an important and intriguing immunological and chemotherapeutic area of research.

The centre of Rees's work has been, throughout, NIMR; an important stage was when (1969) he was given the task of developing there his own Laboratory for Leprosy and Mycobacterial Research. Besides being engaged in basic investigations, and in the questions thrown up from field work, the Laboratory

0305–7518/82/053243 + 05 $01.00

has been the co-ordinating centre for Medical Research Council-participating projects in Malaya, Ethiopia, India and elsewhere. Of these the first and most important was the Leprosy Research Unit, Sungei Buloh, set up in 1957 by Rees, under his direction and sponsored by the MRC and the Malaysian Ministry of Health. He visited India a few years ago, at the invitation of the Indian government, to advise on many aspects of leprosy. A continuing connection with leprosy research in India is the link scheme between the NIMR and the Central JALMA Institute for Leprosy in Agra. This scheme (sponsored in the UK by The Overseas Development Administration) is run jointly by Rees and the Director of JALMA, Dr K V Desikan, and encourages collaborative research and exchange of personnel between the two Institutes.

Rees has advised upon and stimulated work in numerous other projects, including some in the USSR and China. Many leprosy research workers from overseas, scientists and technicians, owe part at least of their expertise to the training facilities provided at Mill Hill. Many researchers have been encouraged in their projects. The international aspect of Rees's work is recognized by the Laboratory being also a World Health Organisation Collaborating Centre for Reference and Research on *M. leprae*. He has participated as a 'founder member' in two of the Steering Committees of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, IMMLEP and THELEP, dedicated, respectively, to the development of a leprosy vaccine and to the improvement of leprosy chemotherapy. A further involvement in leprosy research has been his chairmanship of the LEPRA Medical Advisory Board, which sponsors research programmes in Britain and elsewhe

Rees has also acted on Doull's plea for drawing in many young scientists of different backgrounds into leprosy research: one should mention particularly Philip Draper, Michael Waters, John Pearson and Gordon Ellard. Students, too, have been a source of new blood, fired by his introduction to the subject. To all these international and national activities Rees has brought his remarkable organizing ability; characteristic determination, patience, sound judgment and modesty; as well as scientific astuteness. One of his extraordinary talents is the ability rapidly to switch attention and memory from one to another of the very varied topics raised by the stream of visitors (and telephone callers!) to Mill Hill, and then immediately to concentrate on detailed technical problems of his own laboratory colleagues.

With all this stimulatory and administrative leadership, Rees has never abandoned bench work. The early tissue-culture contribution has been mentioned. Space permits mention of only a few of the subsequent investigations in leprosy which he has carried out, or in which he has played a prominent part. Partial immunosuppression produced by thymectomy plus irradiation of mice was observed to increase their susceptibility and to allow dissemination of infection when *M. leprae* was administered by the Shepard footpad technique (1966); in normal mice infection remains local and limited. This new model has proved of

great value. Thus the enhanced infection makes it possible to detect small numbers of live *M. leprae* among large numbers of dead organisms (valuable for following the progress of chemotherapy). It also provides a somewhat better model for studying the pathology of the infection than does the earlier model in normal mice.

A technique was introduced for following the progress of treatment of leprosy, using the staining morphology of sampled bacilli (1966); the Morphological Index is now widely used as a quantitative measure of viability of *M. leprae* suspensions. Proof was obtained that *M. leprae* could develop resistance to dapsone during treatment (1964), thus establishing a requirement for combined chemotherapy (as with tuberculosis); later, the existence of primary resistance was observed (1977). *M. leprae* was seen to reside free in striated muscle of patients (1970). An enhancement of macrophage resistance to *M. lepraemurium* and *M. microti* by lymphokine treatment of cell cultures was achieved (1971). New evidence for the airborne transmission of leprosy from the nose, and its risks, were studied (1974).

In recent years the Mill Hill laboratory's activities have included further exploitation of the thymectomized-irradiated mouse model to study pathogenesis (e.g. at the ultrastructural level), as well as immunology and chemotherapy of the disease, including the efficacy of new drugs. The relative profusion of yield from the nine-banded armadillo, compared with man or mouse, has redirected attention to the bacillus itself, permitting new discoveries about the organism and its antigens and their immunogenicity; these studies have been facilitated by the armadillo colony set up by Rees at Porton Down, Salisbury. Thus a refined product for the 'lepromin' skin test has been obtained and successfully tested. *M. leprae* has been shown to have a more lively intermediary metabolism *in vitro* than thought; such studies may offer clues to its normal survival *in vivo* and even the hope of cultivation. Purification and fractionation have made progress towards characterization of specific antigens and constituents, and – perhaps more important – towards the production of a safe and protective vaccine.

While leprosy has been Rees's prime field of activity, he has never lost his earlier interest in tuberculosis. Among his notable contributions are the discovery (1951) of the antituberculous effect in mice (later found also in cultured macrophages) of the well-known nonionic surfactant 'Triton WR-1339'; this led to the synthesis by Sir John Cornforth and his colleagues of a large series of analogues (including Macrocyclon) whose varied effects on tuberculous infection correlated with their structural differences. Another important observation was to draw attention to the aggravation of experimental tuberculosis by cortisone, and to its human implications (1950).

The important service of Rees to medicine and to the community was officially acknowledged by the award of CMG in 1979. One hopes that his retirement, at a time when his vigour is undiminished, will leave him free to

pursue some of his research interests, but will not free him from at least some of his international commitments. His successor, Dr M J Colston, should find the Mill Hill laboratory in excellent shape for developing leprosy research further and in new directions.

From Dr Tore Godal in Norway

I spent the winter of 1969–70 at the NIMR. After lunch, coffee was served in a separate room with soft chairs and a lovely view of the 'green belt'. This peaceful atmosphere, with the smell from a humble cigar, provided the opportunity to ask questions from my daily dose of leprosy scientific literature. On almost every topic, Dr Rees could fill in and present views based on direct personal experience or indirectly via one of his collaborators.

In the international community of leprosy, there has been a continuous discussion on whether leprosy is a disease that follows the same ground rules as other infectious diseases or whether it is a unique, singular disease. This discussion includes almost all aspects of the disease, including whether it is infectious and whether it is caused by a mycobacterium. Together with Shepard, Rees has made outstanding contributions to the creation of a sound scientific basis for the study of leprosy.

The establishment of the morphological index as a measure of bacillary disintegration, the discovery of secondary DDS resistance in 1964, of persisters in the mid-70s and the detection of primary DDS resistance in the late 70s, are all fundamental steps towards the development of rational combined chemotherapy in leprosy. Likewise, studies showing that high-dose DDS did not precipitate reactions more often than low-dose DDS were instrumental in eliminating the low-dose DDS dogma. These clinically orientated projects were made possible by the network of MRC field stations. At AHRI and ALERT in Addis Ababa we benefited greatly when Dr Rees responded positively to our invitation to establish such a unit there.

Nevertheless, to an immunologist the most significant contribution so far by Rees to the science of leprosy at the conceptual level was his discovery of a lepromatous-like disease in mice immunosuppressed by thymectomy and X-ray irradiation and reconstituted by bone-marrow cells, providing for the first time unequivocal evidence that T cells are of key importance in protective immunity to intracellular parasites. The model could also be used to study the pathogenesis of nerve damage in lepromatous leprosy, reversal reactions and detection of persisters.

These contributions, in combination with his continuous wholehearted commitment to the training of scientists from all over the world, both in his own laboratory and at courses abroad, have paved the way to the establishment of leprosy on a respectable scientific base. This has in turn created positive

feedbacks in the scientific community by and large, and no doubt has facilitated the development of international research endeavours such as IMMLEP and THELEP. Together with Dr Shepard, Dr Rees from the very beginning agreed to serve on the Steering Committee of both IMMLEP and THELEP – both of which are very demanding tasks. Moreover, to both scientific working groups, Dr Rees has provided key services, such as screening for persisters in thymectomized mice for THELEP drug trials, supplying *M. leprae* from the armadillo and running the *M. leprae* bank.

We wish him a happy and active retirement, in which his resources both at the bench and in an international context will be available for many years to come.

Lepr Rev (1982) **53**, 249–252

Unique expression of HLA-DR (Ia-like) antigen in the lesions of polar tuberculoid leprosy

MARIAN J RIDLEY & D S RIDLEY
Hospital for Tropical Diseases, London NW1 0PE

Received for publication 11 January 1982

Summary HLA-DR antigen was demonstrated in the skin lesions in leprosy in 11 out of 11 polar tuberculoid (TT) cases, in 3 of 6 near-tuberculoid cases in reaction and in 0 out of 38 other cases covering the spectrum from BT to LL. This antigen is therefore a good marker for the TT group. It is suggested that genetic markers may be associated with the rare TT group alone because, among those susceptible to leprosy, they denote the strong immune response that is needed to sustain this position in the spectrum. Susceptibility has not been explained.

Introduction

Leprosy presents a continuous clinical and histological spectrum[1] which correlates with a continuous gradation of lymphocyte performance.[2] However, a recent study of skin biopsies across the spectrum using the immunoperoxidase technique demonstrated important features which were not continuous.[3] Immunoglobulins, complement and some inflammatory mediators were found to correlate with the bacterial load over almost the whole spectrum, but there was paradoxically a peak at the tuberculoid (TT) pole where bacilli are most scanty. This raised the possibility that the rare TT group might be the only group which did not share the immunological defect of lepromatous leprosy.

These conclusions call to mind the results of genetic studies in leprosy. There is a preferential inheritance of the HLA and HLA-DR_2 marker by patients with tuberculoid (mainly TT) leprosy,[4,5] though the association has been observed only in families. It was less strong (not significant) in a mainly BT group of patients,[6] and there are no known genetic markers associated either with lepromatous leprosy or with leprosy patients as a whole.[4,5,7] These results have been interpreted as supporting the hypothesis of an autosomal recessive trait coding for susceptibility to tuberculoid leprosy which is linked with HLA.[5] Susceptibility to lepromatous leprosy is less likely to be due to a single gene than to multiple factors, genetic or otherwise.[7]

0305–7518/82/053249 + 04 $01.00

In the present paper we reconsider this genetic hypothesis in the light of an immunoperoxidase study across the spectrum of leprosy, using an anti-human HLA–DR antibody raised in the mouse. The antigen thereby detected is HLA–DR, which is considered to be the human equivalent of the rodent Ia antigen.

Patients and methods

Fifty-two patients with leprosy were studied: 11 TT, 8 BT, 5 BB, 5 BL and 10 LL; in addition a number of patients undergoing immunological reactions involving an increase of hypersensitivity were included; this resulted in upgrading from BT to TT in 6, and from BL to BT in 4. Three other patients were downgrading from BT towards BB. Biopsies of skin lesions were fixed in a formalin-mercuric chloride-acetic acid mixture, embedded in paraffin wax, and sections were processed by the immunoperoxidase technique.

The indirect peroxidase method was used. Ia antibody (supernatant) was diluted 1/4 in Tris buffer for optimal demonstration as determined by positive staining of Langerhans cells. The sites of binding of the antibody were revealed by peroxidase conjugated rabbit anti-mouse Ig (Mercia-Brocades) diluted 1/20 with Tris buffer plus 0.03 ml/10 ml of normal human serum diluted 1/25 with Tris, in order to block any reactivity against human immunoglobulin.

Results

All 11 lesions of TT leprosy and 3 of the 6 BT reactions resulting in enhanced immunological status (BT–TT) had positive HLA–DR staining cells. The cells were of dendritic appearance and were seen in the dense lymphocytic cuff around the epithelioid cell mass of the granuloma. Langhans giant cells at the periphery of the granuloma were also positive. The material was finely granular and located mainly at the boundary of the cell. None of the other 38 lesions ranging from BT to LL contained positively stained cells. Thus, apart from some near-tuberculoid cases in reaction, Ia-like antigen was unique to the TT group.

Discussion

We do not suggest that the HLA–DR antigen demonstrated here represents the whole of the HLA–DR antigen present in leprosy lesions. Ia antigen is present on surface membranes, though in skin the detected antigen may be intracytoplasmic.[8] The immunoperoxidase technique is adapted mainly for the detection of intracytoplasmic factors. The results demonstrate an antigen which may

represent either intracytoplasmic synthesis or specific localization within cells. Recognition by primed T cells of soluble or disintegrated antigens, as in a TT granuloma, depends on binding or processing by a subpopulation of Ia positive cells.[9] Our results suggest that this sub-population is included amongst cells identified by the immunoperoxidase technique.

The genetic constitution of our patients is not known, but the linkage of HLA–DR antigen with the granuloma of the strictly defined TT component[10] of the broader tuberculoid group was clear cut. This could be interpreted in more than one way. If the Ia phenotype is regarded as the expression of an immune response gene it would imply that this gene, under the conditions of our study, constitutes a reliable marker for the extreme polar tuberculoid group while it is absent from the remainder of the patients who contract leprosy. On the other hand our series of HLA–DR positive TT patients included a small group that had upgraded from BT as a result of a severe reaction reflecting an increase of delayed hypersensitivity. If patients can on occasion acquire Ia-like (HLA–DR) antigen, they can presumably also on other occasions lose it. This alternative is the more likely in the light of experimental evidence that Ia is labile, and depends on the stimulus.[8,11]

It would appear that immunoperoxidase HLA–DR antigen might be a useful marker for classification, and in connection with future genetic studies. Its relationship to the genetic make-up of leprosy patients needs to be elucidated, but the present results suggest that the association of tuberculoid leprosy with HLA–DR2 might indicate only that a strong immune response is necessary to sustain the polar tuberculoid group. Patients who are susceptible to leprosy would develop the TT form if they have good immune response genes, the non-tuberculoid form if they do not. This would be consistent both with the genetic findings, and with the strong production of immunological factors in TT despite the low bacterial load.[3]

On this view the nature of the susceptibility to leprosy in a minority of the human race remains to be unravelled. Perhaps one should be looking for genes not primarily involved in the immune response, or for shared antigens which would impair the host's recognition of the leprosy bacillus as a foreign agent.

Acknowledgement

We are grateful to Dr D Y Mason (Oxford) for the supply of Ia-like antiserum and for useful comments, and to Miss Susan Langeveld for valuable technical assistance.

References

[1] Ridley DS, Jopling WH. Classification of leprosy according to immunity. *Int J Lepr*, 1966; **34**: 255–73.

[2] Myrvang B, Godal T, Ridley DS, Fröland SS, Song YK. Immune responsiveness to *Mycobacterium leprae* and other mycobacterial antigens throughout the clinical and histopathological spectrum of leprosy. *Clin exp Immunol*, 1973; **14**: 541–53.

[3] Ridley MJ, Russell DF, Ridley DS. An immunoperoxidase study of immunological factors in skin lesions across the spectrum of leprosy. *Int J Lepr*, 1982; **50**: 11–17.

[4] Eden W van, van Rood JJ. Genetic regulation of immune responsiveness in man. In: Immunological Aspects of Leprosy, Tuberculosis and Leishmaniasis. ed. DP Humber. International Congress Series. *Excerpta Medica*, 1981; 201–213.

[5] Eden W van, Vries RRP de, Mehra NK, Vaidya MC, Amaro JD', Rood JJ van. HLA segregation of tuberculoid leprosy: confirmation of the DR_2 marker. *J Inf Dis*, 1980; **141**: 693–701.

[6] Rea TH, Terasaki PI. HLA-DR antigens in tuberculoid and lepromatous leprosy. *Lepr Rev*, 1980; **51**: 117–23.

[7] Smith DG. The genetic marker hypothesis for susceptibility to lepromatous leprosy. *Hum Genet*, 1979; **50**: 163–77.

[8] Mason DW, Dallman M, Barclay AN. Graft-versus-host disease induces expression of Ia antigen in rat epidermal cells and gut epithelium. *Nature*, 1981; **293**: 150–51.

[9] Abramson SL, Puck JM, Rich RR. Antigen presentation to human T lymphocytes. 1. Different requirements for stimulation by hapten-modified cells vs cell sonicates. *J Exp Med*, 1981; **154**: 1005–15.

[10] Ridley DS. The pathogenesis and classification of the polar tuberculoid group. *Lepr Rev*, 1982; **53**: 19–26.

[11] Beller DI, Kiely J-M, Unanue ER. Regulation of macrophage populations. I. Preferential induction of Ia rich peritoneal exudates by immunologic stimuli. *J Immunol*, 1980; **124**: 1426–32.

Lepr Rev (1982) **53**, 253–260

An appraisal of third complement component (C3) and breakdown product (C3d) in erythema nodosum leprosum (ENL)

K SAHA[1], A K CHAKRABORTY[2], VINAY SHARMA[3] and V N SEHGAL[4]

[1] *Associate Professor, Department of Bacteriology, Gobind Ballabh Pant Hospital, New Delhi;* [2] *Reader, Department of Biochemistry, University College of Medical Sciences, New Delhi;* [3] *Lecturer, Department of Microbiology, Maulana Azad Medical College, New Delhi;* [4] *Professor and Head, Department of Dermatology and Venereology, Maulana Azad Medical College and associated L.N.J.P.N. & G.B. Pant Hospital, New Delhi*

Received for publication 11 January 1982

Summary Sera from 20 patients with erythema nodosum leprosum (ENL) were collected at the first visit, and 4 weeks after successful therapy. The levels of C3, C3d, C1q and C4 were measured in 20 paired samples. Acute phase reactants – alpha-1-antitrypsin (AAT), alpha-2-macroglobulin (AMG) and C-reactive protein (CRP) – were also estimated to monitor the activity of ENL. The mean serum C3 level showed a decrease during ENL, while after remission it showed a significant increase. Even then, the C3 level after remission was less than that in healthy controls. The mean level of C3d increased remarkably during ENL, and this increase persisted in most patients even after the clinical remission. An inverse relationship between C3d and C3 suggests that the determination of C3d forms a better indicator of C3 hypercatabolism during ENL. Clofazimine treatment resulted in a remarkable decrease of C3d, in contrast to those treated with prednisolone and chloroquine. Mean levels of AAT were greatly elevated during ENL but decreased significantly after its clinical remission.

Serum levels of C1q, C4, AMG and CRP did not alter significantly during ENL and also showed no difference in patients on ENL therapy.

Introduction

Erythema nodosum leprosum (ENL) and its association with circulating and tissue deposited immune complexes have been amply demonstrated.[1,2] A few studies have also been made to demonstrate changes in the serum levels of complement components in both lepromatous leprosy and ENL,[3,4] but follow-up studies amongst these patients have not been adequately reported in the

0305–7518/82/053253 + 08 $01.00

literature. Also, very recently, the levels of C3d and Ba, breakdown products of C3 and factor B respectively have been correlated with the clinical manifestations of lepromatous leprosy.[1,5] This report deals with the studies of complement components (C1q, C4 and C3) and its breakdown product (C3d) in 20 patients during and after ENL. We have also monitored the effect of ENL on serum concentrations of acute phase reactants, namely, alpha–1–antitrypsin (AAT), alpha–2–macroglobulin (AMG) and C–reactive protein (CRP).

Materials and methods

Human materials and their clinical profile. Twenty adult patients (mean age 32.6 years, range 22–50 years) attending the Urban Leprosy Centre, National Leprosy Control Programme, Department of Dermatology and Venereology, Safdarjang Hospital, New Delhi, were studied. The diagnosis of leprosy was established in each case according to published criteria.[6] Eight of the 20 patients belonged to borderline (BL) and 12 to lepromatous (LL) leprosy. Duration of illness varied from 2 years to 18 years with a mean of 4.5 years. The diagnosis of ENL in these patients was made on well-formed clinical features.[7] In 9 patients the ENL was recorded for the first time, while in the rest of the patients there had been one to three episodes of recurrence and remission. Prednisolone was administered in 11, clofazimine in 3 and chloroquine in 6 patients in recommended dose schedule.[8]

Two samples of 5 ml venous blood were collected from each patient. The initial sample was collected on the first visit, while the subsequent sample was drawn on clinical remission of ENL 4 weeks later. Sera were separated and stored in small aliquots at –20°C. Sera were also obtained from 15 properly matched controls.

Immunological techniques. Complement components C1q, C3 and C4 as well as acute phase reactants, namely, AAT, AMG and CRP, were estimated in the serum samples by single radial immunodiffusion technique[9] using monospecific antisera and reference standards. Anti-C1q antiserum was obtained from Behring Institute, West Germany. Anti-CRP antiserum was procured from Kallestad Laboratory, USA, while remaining antisera (against C3, C4, AAT, AMG) and their reference standards were procured from Meloy Laboratories, USA. The levels of C3 and C4 as well as AAT and AMG were expressed as mg/dl of serum. The concentrations of C1q and CRP in the samples were compared with the WHO reference standard serum 67/97 and a locally obtained serum containing a high titre of C-reactive protein respectively. These were expressed in units/dl taking the abovementioned standard sera as 100 units/dl. For quantitation of C3d fragment a two-step immunochemical procedure was used.[10] In brief, 0.2 ml of serum samples were mixed with 0.2 ml of polyethylene glycol 6000 (PEG, BDH, England; final concentration 11%). The

mixture was left at 4°C for 3 hr and then centrifuged for 30 min at 1200 g to precipitate native C3 and C3b. With D antigen-specific antiserum (Central Laboratory, Amsterdam), the concentration of C3d was measured in the supernatant by radial immunodiffusion. The standard reference curve was obtained with pooled fresh sera previously activated with insulin (2mg/ml) for 1 hr at 37°C and then treated with PEG (final concentration 11%). The C3d levels in the test sera were expressed as units/dl taking pooled serum control as 100 units/dl.

The data were analysed and evaluated statistically using paired *t*-test.

Observations

Mean serum levels of the complement components (C1q, C3, C4) and C3d during ENL and after its subsidence are shown in Table 1. Increased catabolism of C3, the key substance of the complement system, during the episode was evident by the significantly low levels of C3 as compared to healthy controls. Furthermore, there was a four-fold increase in the ratio of C3d to C3 (Table 1), and a negative relationship between C3 and C3d levels ($r = -0.36$, Fig. 1). In contrast, C1q and C4 levels did not show any variation during ENL.

The levels of acute phase reactants during and after ENL are given in Table 2. The mean level of AAT was very high during the episode and it showed a statistically significant decrease (23% fall, $t = 2.55$, $p < 0.05$) a month later. The mean levels of AMG and CRP, on the other hand, did not vary appreciably in the paired samples.

Table 1. Profile of complement components and C3 breakdown product, C3d in healthy subjects and in lepromatous patients during erythema nodosum leprosum and after remission.

Complement components	Serum concentration* (mean ± S.D. (range)		
	Healthy subjects	Erythema nodosum leprosum	
		During	After remission
C3	211 ± 38 (101–300)	97 ± 23 (70–150)†	116 ± 25 (70–170)†
C3d	63.5 ± 35 (75–127)	132 ± 74 (28–285)‡	135 ± 75 (33–264)‡
C1q	137 ± 48 (75–215)	153 ± 64 (65–300)‡	168 ± 46 (88–280)‡
C4	31 ± 10 (20–57)	33 ± 10 (12–55)‡	36 ± 12 (12–70)‡
Ratio of C3d:C3	0.30	1.33	1.32

*Serum concentrations of C3 and C4 were expressed as mg/dl, those of C3d and C1q as units/dl.

†Difference statistically significant ($p < 0.05$).

‡Differences statistically not significant.

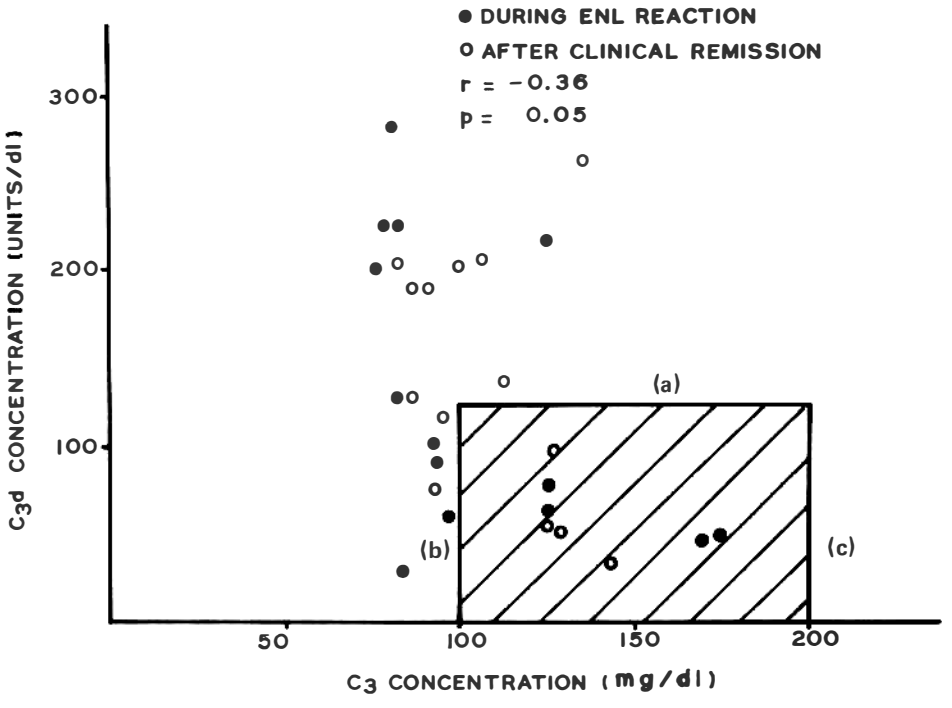

Figure 1. Inverse relationship between serum concentrations of complement component C3 and its breakdown product, C3d during ENL and after clinical remission. Shaded area indicates (a) normal upper limit of C3d level, (b) normal lower limit of C3 level in sera from healthy subjects, (c) mean C3 level in sera from healthy subjects.

Table 2. Profile of acute phase reactants in healthy subjects and in lepromatous patients during erythema nodosum leprosum and after its remission.

Acute phase reactants	Serum concentration* (mean ± S.D. (range)		
	Healthy subjects (15)	Erythema nodosum leprosum (20)	
		During	After remission
Alpha-1-antitrypsin (AAT)	225 ± 85 (35–290)	434 ± 125 (210–600)†	334 ± 123 (180–590)†
Alpha-2-macroglobulin (AMG)	284 ± 89 (150–335)	283 ± 100 (105–475)‡	249 ± 100 (95–430)‡
C-reactive protein (CRP)	Not detected	38 ± 34 (0–100)‡	37 ± 42 (0–125)‡

*Serum concentrations of AAT and AMG were expressed as mg/dl, those of CRP as units/dl.

†Difference statistically significant ($p < 0.05$).

‡Difference statistically not significant.

Table 3. Correlation of the profile of acute phase reactants, complement system and clinical picture with three drugs used in the therapy of erythema nodosum leprosum.

				Changes in sera following clinical remission of ENL		
		Clinical remission of ENL		Acute phase reactant	Complement and its breakdown product	
Drug	Patients (*n*)	(week)	(*n*)	% Decrease of alpha-1-antitrypsin	% Increase of serum C3 level	% Change in serum C3d† level
Prednisolone	11	1st	6	11	17	20 (rise)
		2nd	5*			
Chloroquine	6	1st	3	43	13	42 (rise)
		2nd	3*			
Clofazimine	3	1st	3	32	22	70 (fall)

*One patient in each group showed only partial clinical relief.

†C3d levels were estimated in 8 cases on prednisolone, 3 cases on chloroquine and 3 cases on clofazimine therapy.

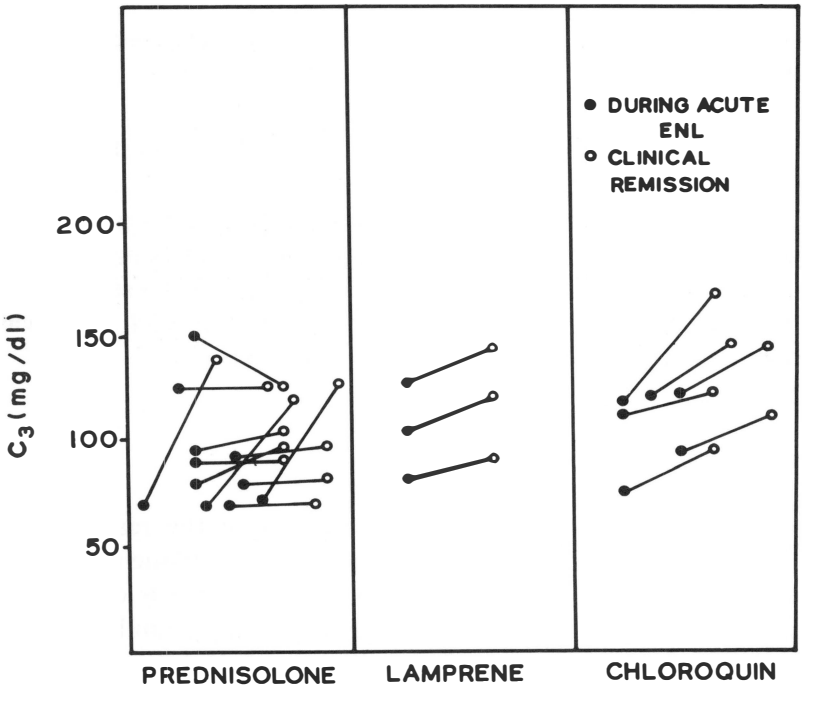

Figure 2. Effect of different drugs used in ENL on the serum concentration of complement component C3 in patients with ENL.

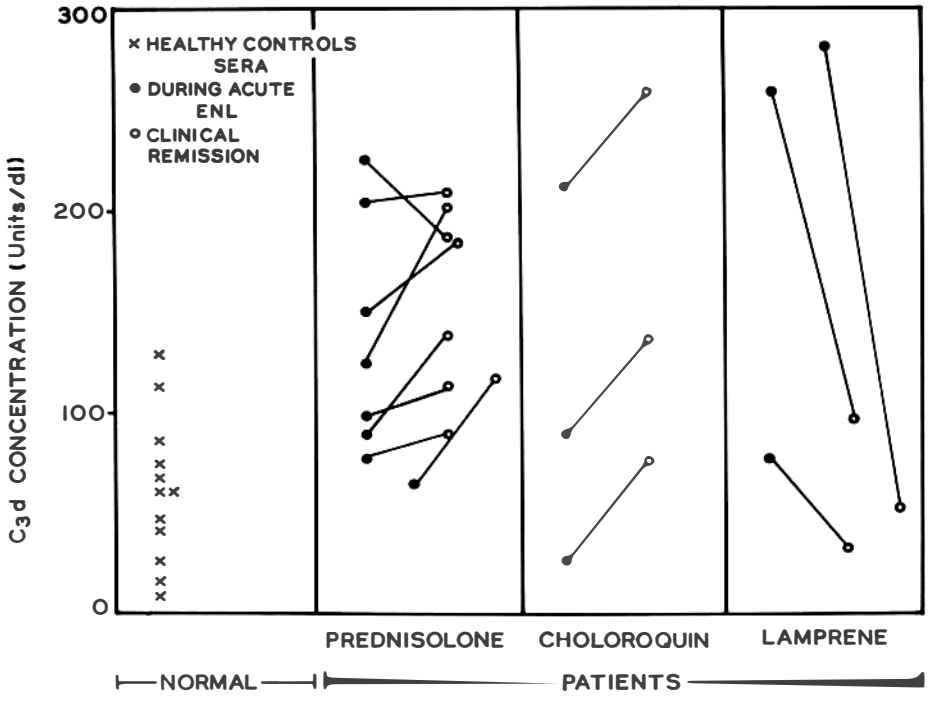

Figure 3. Effect of different drugs used in ENL on the serum concentration of C3d in patients with ENL.

The results of the drugs used in ENL and their effect on the profile of complement and acute phase reactants, are depicted in Table 3. It is apparent that the complement component C3 showed an increased concentration after recovery from ENL in all the treated groups, the effect being marked in those on clofazimine (Fig. 2). Similarly, the effect of drugs on the serum C3d concentration is shown in Fig. 3. Further, a significant fall in AAT levels was noticed in patients on chloroquine and clofazimine (Table 3).

Discussion

Activation of the complement system occurring in the reactionary form of leprosy amplifies inflammatory reaction and enhances tissue damage. This is an important feature of the ENL reaction.[1,5,11] Normal levels of C1q, C3 and C4 in healthy adults from the same socio-economic background as the patients of present series were 137 ± 48 units, 211 ± 38 mg and 31 ± 10 mg per dl of serum respectively. The mean concentration of C3 component was significantly lower in the sera of our patients collected during the reactionary phase than in samples collected after clinical remission 4 weeks later, whereas the levels of C1q and

C4 components varied only marginally (Table 1). Furthermore the decrease in C3 levels in comparison to the normal levels (211 mg/dl) was striking both during ENL (97 ± 23 mg/dl) and after clinical cure (116 ± 25 mg/dl). Many attempts have been made to demonstrate changes in serum complement levels in ENL.[1,3,4,5] Srivastava[4] showed a significant reduction of C3 component with normal C4 level in these patients, indicating involvement of the alternative pathway of complement activation. Bjorvatn *et al.*[1] demonstrated increased level of the C3 breakdown product, C3d in the plasma of 70% of patients with ENL and in only 18% of patients without reaction. Saha & Chakraborty[5] also suggested the activation of complement by the alternative pathway in ENL patients, for they had observed a significant rise of Ba, the breakdown product of factor B in the presence of a fall of C3 level. In another study[3] a fall in complement levels (CH50 and C3) was noticed during the third and fourth months in lepromatous patients with significant proteinuria, whereas C4 levels were normal. These earlier studies and the present one reinforce the view that complement activation during ENL occurs mostly through the alternative pathway. Furthermore, the correlation coefficient *r* (C3d *vs* C3) in our patients was similar to that observed in a study involving patients with membranoproliferative glomerulonephritis,[10] where it was suggested that the detection of breakdown products of C3 gives a fair index of complement system involvement.

The assessment of C3 level appears significant in evaluating immune complex deposits. This view is supported by the observed deposition of C3 components in various parts of the body namely, the dermis, testes, peripheral nerves glomerular and tubular basement membranes of the kidney in ENL (unpublished data).

The C3 level after remission of ENL rose, ranging from 13 to 22% during therapy (Table 3). The levels of early complement components, C1q and C4 remained unaltered. Clofazimine appeared to decrease the level of C3d, a breakdown product of C3, suggesting that this drug probably interferes with the breakdown of C3 and eliminates C3d from the circulation, while the situation is reversed with prednisolone and chloroquine.

The monitoring of acute phase reactants revealed a considerable elevation of serum AAT levels in the early phase of ENL, followed by a significant fall 4 weeks later. These observations are in keeping with those reported earlier.[12] Further, it is believed that AAT is released during the active phase of leprosy, and that it counteracts various endogenous as well as exogenous proteases.[13] It is interesting to note that AAT levels were markedly elevated in the early phase of ENL, but showed a significant decrease following remission. In patients treated with chloroquine and clofazimine this decrease was greater than in those on prednisolone (Table 3). The mean level of AMG, which also binds trypsin, plasmin and thrombin, remained unaltered in ENL, while it showed a considerable fall after remission (Table 2). It is believed that AMG participates in acute phase reactions.[14] CRP is another important acute phase reactant present in all

types of leprosy, but is highly positive (97%) in ENL.[4,15] Our study demonstrated its presence in all paired samples though its concentration did not show a significant decline after subsidence of ENL. It is now known that C-reactive protein is a precursor for protein P, a minor component of all amyloid.[16]

References

[1] Bjorvatn B, Barnetson FS, Kronvall GK, Zubler RH, Lambert PH. Immune complexes and complement hypercatabolism in patients with leprosy. *Clin exp Immunol*, 1976; **26**: 388–96.

[2] Wemambu SNC, Turk JL, Waters MFR, Rees RJW. ENL – A clinical manifestation of the Arthus phenomenon. *Lancet,* 1969; **ii**: 933–5.

[3] Kumar B, Ganguly NK, Kaur S, Sharma S, Chakravarty RN, Mahajan RC. Complement profile in leprosy. *Leprosy in India*, 1980; **52**: 217–22.

[4] Srivastava LM, Agarwal DP, Goldee HW, Rohde R. Biochemical, immunological and genetic studies in leprosy. II. Profile of immunoglobulins, complement components and C-reactive protein in sera of leprosy patients and healthy controls. *Tropen Med Parasit*, 1975; **26**: 212–18.

[5] Saha K, Chakraborty AK. Serum complement profiles in human leprosy and its comparison with immune complex diseases. *Int J Lepr*, 1977; **45**: 327–37.

[6] Ridley DS, Jopling WH. Classification of leprosy according to immunity. *Int J Lepr,* 1966; **34**: 255–73.

[7] Sehgal VN, Rege VL, Masuarruhans MF. Pattern of reactions in leprosy. A clinical appraisal. *Lepr India*, 1977; **49**: 221–8.

[8] Sehgal VN. Clinical leprosy. 1st ed. Sahibabad (UP): Vikas, 1979; 52–8.

[9] Mancini G, Carbonara AC, Heremans JP. Immunochemical quantitation of antigens by single radial immuno-diffusion. *Immunochemistry*, 1965; **2**: 235–54.

[10] Perrin LH, Lambert PH, Miescher PA. Complement breakdown products in plasma from patients with systemic lupus erythematosus and in patients with membranoproliferative and other glomerulonephritis. *J Clin Invest*, 1975; **56**: 165–76.

[11] Bullock WE. Leprosy: A model of immunological perturbation in chronic infection. *J Inf Dis*, 1978; **137**: 341–54.

[12] Agarwal SK, Saha K. Serum alpha-1-antitrypsin in various forms of leprosy. *Indian Jour Med Res*, 1978; **68**: 136–9.

[13] Hermann G, Miescher PA. Differentiation of leucocytic fibrinolytic enzymes from plasmin by the use of plasmatic proteolytic inhibitors. *Int Arch Allergy*, 1965; **27**: 346–54.

[14] Housley J. Alpha-2-macroglobulin levels in diseases in man. *J Clin Path*, 1968; **21**: 718–22.

[15] Sen Gupta U, Sinha S, Ramu G. Immunological assessment of sera of leprosy patients. *Leprosy in India*, 1979; **51**: 43–8.

[16] Sell S. Immunology, immunopathology and immunity. 3rd ed. Harper & Row: 276. 1980.

Lepr Rev (1982) **53**, 261–264

Simple plantar ulcers treated by below-knee plaster and moulded double-rocker plaster shoe – a comparative study

D J PRING* & N CASIEBANCA†
**Surgeon to Leprosy Mission Hospital, Anandaban, PO Box 151, Kathmandu, Nepal; †Senior Medical Officer TLM Salur, India*

Received for publication 16 December 1981

Summary Fifty-five simple plantar ulcers in patients with Hansen's disease were treated in plaster for 6 weeks as outpatients. A conventional below-knee plaster of Paris (BK POP) was applied to 24 ulcers. Eighteen ulcers healed, 3 nearly healed and 3 failed to heal. Thirty-one ulcers were treated with a moulded double plaster of Paris (MD POP) shoe, 18 were healed, 8 almost healed and 5 failed to heal. The MD POP shoe was better accepted by patients and proved more economical; it also provides an acceptable and effective alternative to the BK POP for the outpatient treatment of simple plantar ulcers.

Introduction

Simple plantar ulcers heal rapidly with rest. The below-knee (BK) plaster has been used for many years as a means of providing rest for the ulcer to heal yet still allowing ambulation.[1] It can be applied in the outpatient clinic and admission to hospital is not required. Using this method good results have been reported.[2] However, plaster is both expensive and heavy; consequently a smaller plaster shoe has been designed which is cheaper and lighter. The results of this plaster shoe are compared with traditional BK plaster.

Materials and methods

Fifty-five simple plantar ulcers occurring in 47 patients suffering from Hansen's disease were admitted to the study. We defined a simple plantar ulcer as an ulcer on the plantar surface of the anaesthetic foot which did not involve either the underlying bone, joint or tendon. The patients were randomly divided into two groups. One group was treated with a conventional padded below-knee plaster, the second group with a padded moulded double-rocker plaster shoe.

0305–7518/82/053253 + 04 $01.00

Plasters were applied over a small magnesium sulphate glycerine and acriflavine dressing to the ulcer and removed after 6 weeks. The majority of patients were treated as outpatients.

A moulded double-rocker plaster shoe consists of a double-rocker foot board which is applied under the foot. The arch is packed with wet plaster as a moulded platform around the foot to produce a shoe. It extends high enough up the foot to prevent removal but not above the malleoli so as to avoid pressure sores. Ankle movement is free. The toes are covered. Patients were instructed to walk with an elephant gait lifting their foot off the ground and replacing it flat rather than the usual walking pattern of heel strike, stance and push off, as this lessens the mechanical forces on the foot. Patients with foot drop, fixed inversion deformity, rocker bottom or short feet were excluded from the trial as these feet are not suitable for treatment with an MD POP shoe.

The site, size and depth of each ulcer were recorded as well as its duration, any previous ulcer at the same site and the state of the local skin. The ulcers were divided into deep ulcers involving muscle, and superficial ulcers involving only the subcutaneous fat. This division was rather subjective as often fibrous tissue had replaced the muscle and fat at the ulcer site.

After removal of plaster the ulcer site was inspected. If healed, patients were advised to resume full walking cautiously over the following week. Both at the time of application and removal of plasters intensive health education was given on foot care. Patients were taught the principles of daily foot inspection, foot soaking and scraping, and the importance of the regular wearing of soft-lined chappels.

Results

Thirty-one ulcers were treated with an MD POP shoe and 24 with BK POP. Of the 31 ulcers treated with MD shoe 18 (58%) were fully healed after 6 weeks, 8 (26%) were nearly healed (incomplete epithelial healing ulcer which rapidly healed within a few days of further rest) and 5 (16%) failed to heal. Of the 24 treated by BK POP 18 (75%) fully healed, 3 (12.5%) were nearly healed and 3 (12.5%) failed to heal.

The average duration of each ulcer prior to plaster application was 11.9 months (range 1 week to 7 years). Twenty-six (84%) ulcers were either recurrent ulcers or had surrounding callous and scar, 21 (87.5%) ulcers were first ulcers with good local skin. In 10 ulcers this information was not recorded. The distribution of the sites of each ulcer is shown in Fig. 1. The size and depth of ulcers is shown in Table 1. There was a greater preponderance of deep ulcers in the MD POP group.

Of the 11 ulcers which were nearly healed on removing plaster 9 were originally deep ulcers and only 2 superficial; 3 were size '1', 7 size '2' and 1 size '3'.

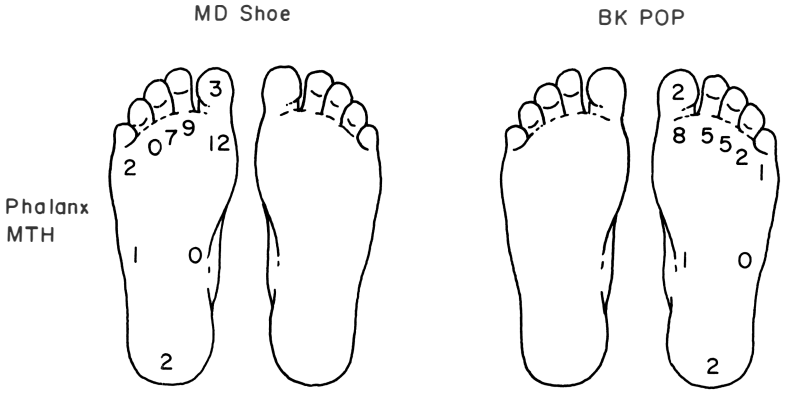

Figure 1. Distribution of ulcers. (NB some ulcers involved more than one site.)

Analysis of the 8 ulcers that failed to heal in 6 weeks reveals one superficial heel ulcer treated by MD POP shoe which was still superficial after 6 weeks. One superficial fore foot ulcer treated with MD shoe was healing after 6 weeks and the MD POP shoe was reapplied for a further 4 weeks after which the ulcer was healed. Another deep ulcer treated by MD shoe was healing but the patient refused further plaster and 5 months later the ulcer was still superficial.

Two ulcers, one treated by MD POP shoe and the other with BK POP had excessive granulation covering the ulcer and were treated with silver nitrate and healed.

One ulcer treated with BK POP was healing after 6 weeks but the patient was advised to have a multiple metatarsectomy to more evenly distribute the forces of weight bearing over the foot. Two ulcers, one treated with MD POP shoe the other with BK POP were probably misdiagnosed originally as simple ulcers when in fact they were complicated. Both were advised to have a dorsal incision and excision of the affected metatarsal heads.

Discussion

Simple plantar ulcers will heal rapidly if kept clean and rested. Because of the immense size of the problem it is neither practicable nor necessary to admit

Table 1. Size, depth and number of ulcers

	Diameter* (no.)			Depth (no,)	
	1	2	3	Superficial	Deep
MD POP	21	9	1	11	20
BK POP	15	6	3	13	11

*Diameter: 1 = 0–½ in.; 2 = ½–1 in.; 3 = 1–2 in.

patients to treat these ulcers. Yet expecting a patient to stay at home resting in bed for several weeks is frequently impracticable as he is unable to earn a living for himself or his dependants.

Plaster treatment of simple plantar ulcers is a means whereby the patient can remain mobile while at the same time providing rest and a clean dressing for his ulcers. There are two criticisms of plaster treatment. First the patient may associate healing of his ulcer with plaster rather than with foot care and so he continues to reulcerate. We therefore at all times subject the patient to intensive health education regarding foot care. Secondly plaster immobilization results in disuse osteoporosis of bones, which renders them liable to fractures after plaster removal. Pain in the sensitive foot usually protects the osteoporotic foot from fracture and the normal patient limps for a few days after plaster removal. However, the patient with the anaesthetic foot has no such inhibitions so must be warned to gradually increase his daily walking and not immediately return to his old walking habits, risking both micro- and macro-fractures.

The BK POP immobilizes the foot more than the MD POP shoe which does not immobilize the ankle, subtalar or mid-tarsal joints which probably explains the difference in results with ulcers treated by BK POP rather than the MD shoe. However, the results using the MD shoe are not that much inferior – 87.5% compared with 84% when the healed and nearly healed are grouped together. The MD shoe is more acceptable to the patient, cheaper to apply and, more important, likely to cause less disuse osteoporosis than the BK POP and therefore the risks of fracture should be reduced.

Too few heel ulcers were included in the study to conclude how effective the MD POP boot is in healing these difficult ulcers.

References

[1] Fritischi EP. Care of the foot. In: Thangaraj RH, ed. *A manual of leprosy* 2nd edn Delhi: The Leprosy Mission, 1980; ch. 15.

[2] Price EW. *Lepr Rev*, 31.3.1960.

Lepr Rev (1982) **53**, 265–269

Malignant degeneration in chronic ulceration of the leg and foot in leprosy patients; two case reports

J G ANDERSEN
All Africa Leprosy and Rehabilitation Training Centre (ALERT)
P.O. Box 165, Addis Ababa, Ethiopia

Received for publication 20 August 1981

Summary The development of squamous cell carcinoma in long-established ulcers is described in two patients with leprosy, one on the lower leg in a patient with borderline-tuberculoid (BT) leprosy and the other on the sole of the foot in a patient with lepromatous (LL) leprosy. Although sometimes stated by clinicians to be rare, and infrequently reported in the literature, it is suggested that malignant change in chronic ulcers in leprosy may be found more often if patients are examined with care and the possibility kept in mind.

Introduction

Writing in 1964, Job and Riedel[1] commented that carcinoma arising in plantar ulcers in leprosy was extremely uncommon; they were in fact unable to find reports in the literature at that time. They suggested, however, that more cases might be recorded if careful attention were paid to the examination of ulcers and the possibility of malignant change kept in mind, and two years later Riedel published an additional note on malignancy in plantar ulcers, describing four cases of squamous carcinoma arising during a period of two years in one centre in India.[2] Although it is well known to surgeons and others that chronic ulceration occasionally gives rise to malignant change, it is therefore perhaps significant that a survey of the leprosy literature at the present time does not suggest that this is a common event in chronic ulcers of the leg and foot in leprosy. However, experience from this centre in previous years indicates that the complication is perhaps commoner than the literature suggests and we believe that if competent examiners look for this development, it will not be a rarity. We report here two cases in which malignant change occurred in ulcers on anaesthetic skin areas in patients with long-standing leprosy.

0305–7518/82/053265 + 05 $01.00

Case reports

First patient: a middle-aged lady. Clinical diagnosis: lepromatous leprosy, negative on slit-skin smear examination, under treatment with DDS since 1960. She had for a number of years suffered from ulceration with smouldering osteomyelitis of both forefeet. Both plantar surfaces have been anaesthetic for several years.

In April 1978 the condition of the left foot was considered serious enough to urge her to accept a formal forefoot amputation, while on the right side it was considered feasible to perform a pretalar amputation, followed by tibio-calcaneal fusion with 45 degrees rotation of calcaneum. She refused operation.

In May 1978, the septic condition of the left foot had advanced to the degree where a formal below-knee amputation was considered necessary. The condition of the right foot appeared reasonably stable, and the previous advice was repeated. Once again she refused.

In November 1978 a firm clinical diagnosis of secondary carcinoma of the

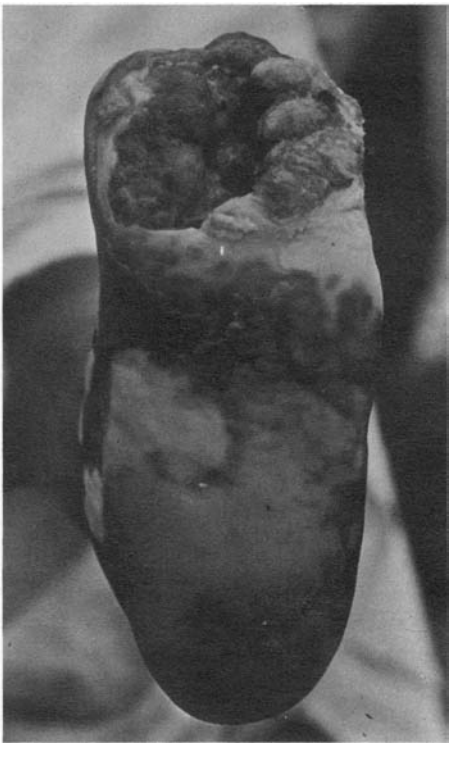

Figure 1. First patient. The ulcer as seen in November 1978, had increased in size and depth, with gross undermining. After removing pus and necrotic tissue red everted edges were revealed.

left foot was made. When this was explained, she accepted below-knee amputation. The right foot was only slightly worse. It was considered possible to repeat the previous offer of a limited ablation of the fore- and mid-foot, but she still hesitated to accept this offer.

On first examination the ulceration of the left forefoot was deep, with exposed sequestra and necrotic tissue. The edges of the wound were sloping with no evidence of hyperkeratosis or hypertrophy, and with no significant undermining. X-ray examination demonstrated bone absorption and osteomyelitis with sequestration, but with no signs of malignancy.

On the second examination, the situation was much the same, but the ulceration had progressed and the radiological picture was worse. There was significant undermining of the edges, but still no signs of malignancy.

In November 1978 the picture was radically and dramatically different. The ulcer was very deep with gross undermining (Fig. 1). The whole area was covered with pus and necrotic tissue. When this had been cleared off, thick, raised, red everted edges were seen, a picture strongly suggestive of carcinoma. At no time were any significantly enlarged regional lymph nodes felt. Pathology report: squamous cell carcinoma.

Second patient: a middle-aged man. Clinical diagnosis: borderline-tuberculoid leprosy; slit-skin smears negative. First registered in 1965. He had for the last seven years suffered from repeated attacks of blister formation and eventual ulceration of the anterior surface of the lower leg on an area of extensive anaesthesia. He received repeated treatment with bland local applications. Five months ago he noticed that the ulcer increased in size and depth. Local and systemic antibiotics had no effect.

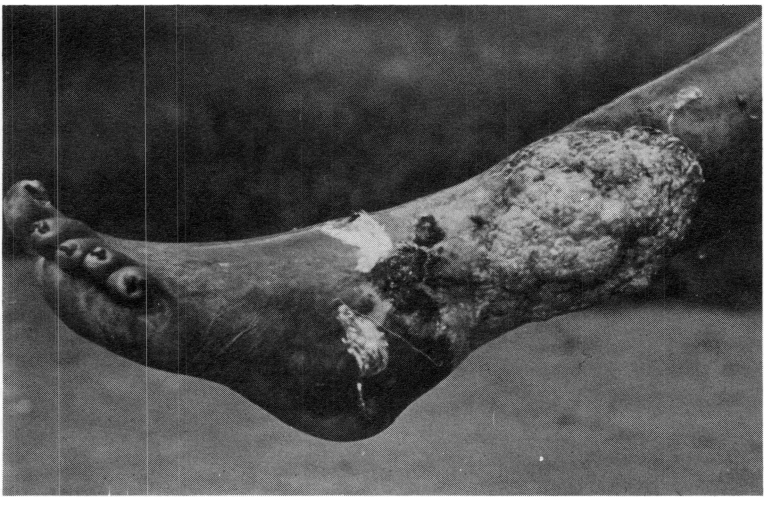

Figure 2. A large fungating mass on mid-shin, extending in all directions below skin surface.

On examination the left lower leg was shiny with anaesthetic, atrophic skin. A large fungating mass was seen on mid-shin, apparently extending in all directions below the skin surface. The mass was adherent to deeper structures. No significant enlargement of regional lymph nodes was found. X-ray examination showed a hazy periosteal reaction of considerably larger extent than the actual ulcer.

A diagnosis of secondary carcinoma was made clinically. The patient accepted the offer of below-knee amputation. Pathology report: squamous cell carcinoma with involvement of periosteum.

Discussion

An increased incidence of malignant skin tumours in patients with lepromatous leprosy has been reported[3] from a large series of patients in Brazil, but a recent review of the incidence of cancer of all types in patients with leprosy[4] did not suggest a positive association. The second patient described here clearly had an ulcer on a site (lower leg) typical for the 'tropical' or 'phagedenic' ulcer, in which squamous cell carcinoma is said to occur in 9% of all cases.[5] We have been unable to find any comparable figure for the likely incidence of malignant change in plantar ulcers in leprosy. In both cases described in this report, long-standing secondary infection appears to have been an important factor and there was certainly no evidence that specific infection with leprosy played any part. Resultant anaesthesia on the other hand may well have caused a diminished appreciation of pain in both patients, thus contributing to delay in their seeking treatment at an early stage. It may be of interest to recall that many tropical or phagedenic ulcers are extremely painful.

Ulcers undergoing malignant degeneration tend to produce a fungating mass with, in the initial stages, only radiologically non-specific periosteal reaction. At a later stage one may see an almost punched out lytic lesion in the tibia. Malignant degeneration in a plantar ulcer in leprosy is likely to remain undiagnosed for a long time, unless specifically looked for. The reason may be that the anaesthetic, ulcerated foot not only sequestrates the tissue before manifest malignancy becomes obvious, but also that the concomitant poor blood supply does not readily support the growth of malignant tissue. Self-cure, albeit with gross disability and tissue loss, is probably not infrequent. Carcinomata in chronic lower limb ulcers tend to metastasize slowly. Significantly enlarged regional lymph nodes should be left severely alone. It is impossible on clinical grounds to distinguish between metastases and septic enlargement of lymph nodes and attempts to excise them or even to take a biopsy, or to otherwise interfere with them is likely to produce a chronic, fistulating lesion. On the other hand, once the primary focus has been safely removed, septic lymph nodes will settle down and metastases may diminish in size, and even disappear in some cases.

Prognosis for life is excellent in malignant degeneration of ulcers of the lower leg and sole of foot. The obvious treatment is surgical ablation. The actual level of amputation should be determined by the septic condition, the viability of tissue, and the suitability for prosthesis, rather than by the malignant process as such. Fortunately, the lowest convenient amputation often yields as good a result in respect of survival as higher levels of amputation.

References

1 Job CK, Riedel RG. Squamous cell carcinoma arising in plantar ulcers in leprosy. *Int J Lepr*, 1964; **32**: 37–44.

2 Riedel RG. An additional note on malignancy in plantar ulcers in leprosy. *Int J Lepr*, 1966; **34**: 287–8.

3 Michalany J. Malignant tumours of the skin among leprosy patients. *Int J Lepr*, 1966; **34**: 274–86.

4 Purtilo DT, Pangi C. Incidence of cancer in patients with leprosy. *Cancer*, 1975; **35**: 1259–61.

5 Edginton GM, Gilles HM. *Pathology in the Tropics.* 2nd ed. Edward Arnold, 1976.

Lepr Rev (1982) **53**, 271–276

Treatment of leprosy wounds with adhesive zinc tape *

T SÖDERBERG,† G HALLMANS,‡ S STENSTRÖM,†
D LOBO,§ J PINTO,§ S MAROOF,‖ & CLAIRE VELLUT‖
From the Departments of Hand and Plastic Surgery† and Pathology‡, University of Umeå, Umeå, Sweden, Father Müller's Hospital, Mangalore§, India, and Hemerijyckx Leprosy Hospital, Polambakkam‖, India

Received for publication 30 March 1982

Summary In two hospitals in India 90 leprosy patients with a total of 128 ulcers on the soles of their feet were treated with local applications of zinc or gauze soaked in Eusol. The patients were selected on a random alternate basis. The average healing time was shorter for the tape-treated ulcers compared to the gauze-treated ulcers in both hospitals. The zinc tape was easy to apply, could be worn under shoes without causing pressure and was socially acceptable because no bandages were needed.

Introduction

For many years ordinary adhesive zinc tape has been used in the treatment of local wounds.[1–4] The tape has been applied to the wounds in many different ways and has proved valuable in the dissolution and removal of tissue necroses – particularly in the case of burns – and in cleansing infected wounds. Experimental studies in rats comparing the healing times of small excisional wounds treated with gauze sponges or zinc tape have shown that there is a shorter healing time when the tape is used.[5,6] It has been established that zinc plays a part in the wound healing process in man and that such healing is impaired in zinc-deficient animals and man.[7,8] Zinc from the zinc oxide in the tape is dissolved from the adhesive substance and absorbed into granulation tissue and serum.[4]

*Supported by grants from the Swedish Medical Research Council (Project No. 04518) and the Swedish Agency for Research Co-operation with Developing Countries (Project nr 77/44:3).

0305–7518/82/053271 + 06 $01.00

Zinc deficiency is common among patients with burn wounds[9] as well as among patients suffering from leprosy.[10] The treatment method using zinc tape was introduced among leprosy patients for wound treatment in Ethiopia in 1970 by Dr Sten Stenström and in 1976 he reported very good results.[11] The present study was intended to compare the results of the tape treatment method with those of the widely used method of covering the wounds with gauze sponges soaked in Eusol.

Material and methods

Ulcers on the soles of the feet of patients in two leprosy hospitals in India, Father Müller's Hospital in Mangalore, Karnataka State (60 patients) and Hemerijyckx Hospital in Polambakkam, Tamil Nadu State (30 patients) were entered on a register. This was done using special forms which, apart from personal details, occupation, type of leprosy and disability grades (WHO classification), provided the following information about the ulcers:

A Date of formation of ulcer according to the patient.
B Type of ulcer:
  a Superficial: Whole ulcer is visible. No deep sinus. No signs of inflammation. No bone, tendon or capsule seen.
  b Deep: Deeper tissues involved.
  c Complicated: Deep sinus. Obvious clinical signs of infection. Joint, bone, tendon or capsule involved.
C Size of ulcer:
  a Small: Diameter less than 2 cm.
  b Large: Diameter 2 cm or more.
D Location of ulcer.

Two different groups of patients (with non-complicated ulcers) were selected. One group was treated with adhesive zinc tape and a control group was treated with ordinary gauze dressings soaked in different ointments as per the routine followed in the respective hospitals.

The non-porous adhesive zinc tape was made of a plastic web coated with an adhesive substance composed of gum, resin and zinc oxide. The zinc oxide concentration was approximately 30%. The tape was applied directly to the wound surface after soaking and drying the hands and the feet. The tape covered the ulcer and the surrounding skin. It was initially changed daily while the wound secretion was excessive, and less frequently as it decreased. No other bandage was used.

The gauze sponge was soaked with Eusol, applied directly to the wound surface, and kept in place with a bandage around the foot. New dressings were applied as in the case of zinc tape treatment.

The patients were selected on a random alternate basis without taking into consideration either the type or size of the ulcers. All the patients reported here are patients with non-complicated ulcers on their feet and they were all treated in the hospital. Of the 128 ulcers registered, 86 were in Mangalore and 42 in Polambakkam. Among the tape-treated patients in Mangalore, 23 were men and 10 were women, and among the gauze-treated patients in the same hospital 22 were men and 5 were women. All patients in Mangalore wore shoes. In Polambakkam all the tape-treated patients were men and among the gauze-treated patients there were 12 men and 3 women. Eighteen patients wore shoes and 12 did not. The starting date of the treatment (with either tape or gauze) and the date of healing were recorded on the form. The ulcer was accounted healed when complete epithelialization had occurred.

Statistics

The differences between group means for variables were tested using Student's *t*-test for unpaired observations. The test was modified if the variances were significantly different (*F*-test).

Results

The results have been tabulated separately for the two hospitals where the trials were conducted since they were completely independent of each other, though the same registration forms and principles were used. All patients had a disability grade of 1 or 2 (WHO classification) for the feet with ulcers. All ulcers were located on the plantar side of the feet or on the toes. Most of them were located under the head of the first metatarsal bone and on the big toe (Fig. 1).

The average healing time was shorter for the tape-treated wounds compared to the gauze-treated wounds in all groups of ulcers in both hospitals (Figs 2 and 3), although the differences were statistically significant in Polambakkam. No signs of skin sensitization were observed in either the tape-treated or the gauze-treated wounds.

Discussion

The healing time was shorter for tape-treated ulcers compared to similar gauze-treated ulcers. The zinc tape has the following advantages: 1, Shorter healing time. 2, Low cost. 3, Easy application. 4, More convenient for patients: (a) can be worn under shoes without causing pressure; (b) socially more acceptable, no bandages are needed. This is important for out-patients, especially since the bandages are often stigmata of leprosy.

Various factors are responsible for the shorter healing-time achieved with

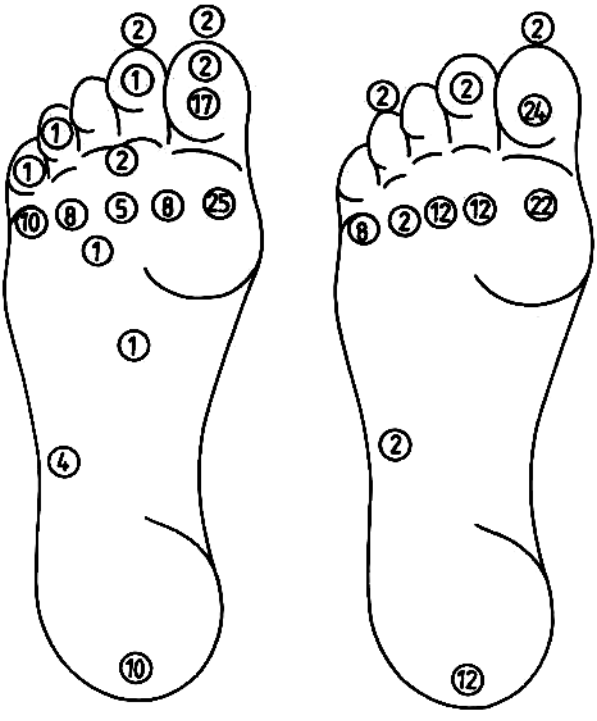

Figure 1. Location of the 86 plantar ulcers in Mangalore (left) and the 42 plantar ulcers in Polambakkam (right) expressed as a percentage of the total number of ulcers in each hospital.

adhesive zinc tape. Zinc tape by virtue of being non-porous and waterproof acts as an occlusive dressing thereby protecting the ulcer and preventing contamination from outside. Necrotic tissue whenever present is dissolved during treatment with zinc tape.[3,12] It has to be emphasized that the adhesive substance must be strongly adhesive to the surrounding skin, otherwise the zinc tape will quickly come away from the wounds. It is generally agreed that epithelialization is fast during occlusive treatment where the epithelium is migrating through an exudate. The risk of infection offered by the same exudate is probably lessened by the liberation of zinc from the zinc tape.[13] The epithelialization progressing in the wound is not damaged when the tape dressing is changed because the tape never sticks to the wound and there is no traumatization during redressing. This can rarely be avoided with other dressings like gauze. Although the gauze dressing may be almost occlusive, a state which is known to be favourable to epithelialization,[14] cotton gauze itself provides a poor environment for epidermal healing.[15] Similar results of differences in healing times between zinc-tape-treated wounds and gauze-treated wounds has previously been observed in rats.[5,6]

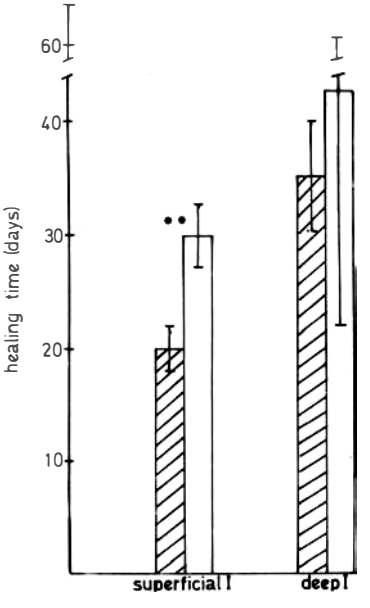

Fig. 2

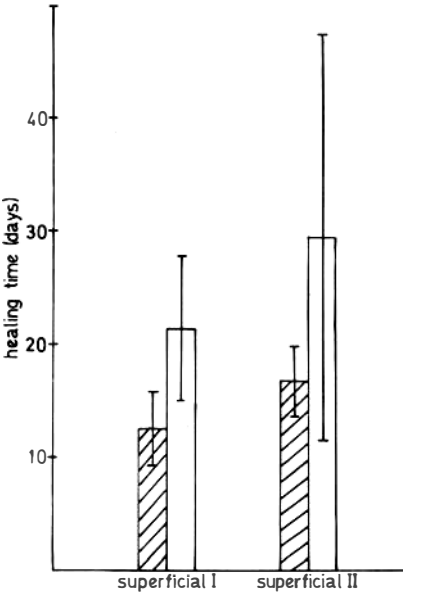

Fig. 3

Figure 2. Wound healing time in days of superficial and deep ulcers treated with zinc tape or gauze in Mangalore. I = Wound area less than 2 cm in diameter. ▨, tape treatment; □, gauze treatment.

Figure 3. Wound healing time in days of superficial ulcers treated with zinc tape or gauze in Polambakkam. I = Wound area less than 2 cm in diameter. II = Wound area more than 2 cm in diameter. ▨, tape treatment; □, gauze treatment.

Zinc from the zinc tape is absorbed into granulation tissue. This may be beneficial for the wound-healing process as zinc is needed for a normal wound-healing process during zinc deficiency.[8] Zinc-tape-treated wounds have been found to have a high collagen content compared with gauze-treated wounds in rats.[6] It was postulated that the high collagen concentration in tape-treated wounds was a result of a decreased liberation of collagenase by the macrophages. Macrophage activity is inhibited by high concentration of zinc.[16]

We have observed that very often the first reaction to the mention of adhesive zinc tape as a treatment for wounds is one of disbelief, lack of interest, or ridicule, or a combination of all three. The results presented here show that zinc tape is of value in the treatment of leprosy ulcers. We are convinced that the main advantage in treating leprosy wounds with zinc tape lies in using the method on out-patients where the benefits of the treatment are most obvious. Patients can be instructed on how to treat their own ulcers with the tape. They can be given pieces to use at home whenever needed. Through the early treatment of ulcers or injuries by the patient himself complications might be avoided, thus preventing mutilation.

References

[1] Widerøe S, Sårbehandling, Oslo. 1925.

[2] Gilje O. Ulcus cruris in venous circulatory disturbances. *Acta Dermatovener Suppl*, 1949; 22.

[3] Stenström S, Bergman G, Bergman S. Wound healing with ordinary adhesive tape. *Scand J Plast Reconstr Surg,* 1972; **6**: 40.

[4] Hallmans G. Absorption of topically applied zinc and changes in zinc metabolism during wound healing. *Acta Dermato-Venerologica*, 1978; **58**: suppl 80.

[5] Hallmans G. Wound healing with adhesive zinc tape. An animal experimental study. *Scand J Plast Reconstr Surg*, 1976; **10**: 1977.

[6] Hallmans G, Hänström L, Lundgren E. The effect of zinc tape upon wound healing in rats. A biochemical, histochemical and histological study. *Scand J Plast Reconstr Surg*, 1979; **13**: 251.

[7] Sandstead HJ, Lanier UC, Shepard GH, Gillespie DD. Zinc and wound healing. Effects of zinc deficiency and zinc supplementation. *Am J Clin Nutr*, 1970; **23**: 514.

[8] Hallböök T, Lanner E. Serum zinc and healing of venous leg ulcers. *Lancet*, 1972; **ii**: 780.

[9] Larsson DL, Maxwell R, Abston S, Dobrokvsky M. Zinc deficiency in burned children. *Plast Reconstr Surg*, 1970; **46**: 13.

[10] Oon BB, Khong KY, Greaves MW, Plummer VM. Trophic skin ulceration of leprosy. Skin and serum zinc concentrations. *Brit Med J*, 1974; **2**: 531.

[11] Stenström S, Hallmans G, De Jongh A, De Wael T. Leprosy wound healing with ordinary adhesive tape. A preliminary report. *Scand J Plast Reconstr Surg*, 1976; **10**: 241.

[12] Hallmans G. Healing of experimentally induced burn wounds. A comparative study of the healing of exposed wounds covered with adhesive zinc-tape and a scanning electron microscope study of the microvasculature of wound healing in the rabbit ear. *Scand J Plast Reconstr Surg*, 1978; **12**: 105.

[13] Hallmans G, Elmros T. Zinc tape treatment of burns infected by pseudomonas aeruginosa. An experimental study on guinea pigs. *Scand J Plast Reconstr Surg*, 1980; **14**: 221.

[14] Hinman CD, Maibach H. Effects of air exposure and occlusion on experimental human skin wounds. *Nature*, 1963; **200**: 377.

[15] Winter GD. Epidermal wound healing under a new polyurethane foam dressing (Lyofoam). *Plast Reconstr Surg*, 1975; **56**: 531.

[16] Zukoski CF, Chvapil M, Carlson E, Hattler B, Ludwig . Functional immobilization of peritoneal macrophages by zinc. *J Reticuloendothel Soc*, 1977; **16**: 6a.

Lepr Rev (1982) **53**, 277–283

Familial clustering of leprosy patients in an Israeli village

D A BARREYRO*, M BARAS, PAMELA SQUIRES, MARCIA WALERSTEIN, YAIR YODFAT & L LEVY
Departments of Comparative Medicine, Family Medicine and Medical Ecology, Hebrew University – Hadassah Medical School Jerusalem, Israel

Received for publication 22 March 1982

Summary In an Israeli community of immigrants from Kurdistan, with a leprosy prevalence of 3.2 per 100, the leprosy patients were found to be clustered in a very few sibships.

Introduction

That leprosy patients may be found in intrafamilial clusters – that is, that patients are found in multi-patient households more frequently than would be predicted by chance – is accepted as fact, and has often been assumed in the design of leprosy-control programmes. Yet, limiting case-finding activities in leprosy-endemic areas to the families of leprosy patients would fail to reveal the large majority of leprosy patients. A study in an area of south India with prevalence of leprosy of 21 per 1,000 found[1] that, although 8% of all families included leprosy patients, the 16% of affected families that included more than one patient accounted for only 30% of all patients. In an area of somewhat lower prevalence of leprosy (6.6 per 1,000) in central India, it was found[2] that 4% of all families included leprosy patients; the 9% of affected families that contained more than one patient accounted for only 18% of patients. No comparable studies have been reported from areas non-endemic for leprosy. Yet the results of such studies could have important implications for the design of leprosy-control activities in those areas.

An opportunity to examine the distribution of leprosy in a community in an area of low prevalence of leprosy was afforded by the presence at one time

*Submitted in partial fulfilment of the requirements for the M.P.H., Hebrew University – Hadassah School of Public Health and Community Medicine.

0305–7518/82/053277 + 06 $01.00

or another in a small immigrant community near Jerusalem of a number of leprosy patients. This study has revealed unmistakable clustering of leprosy patients among intrafamilial contacts, and particularly within sibships.

Materials and methods

In 1951, Jews from four contiguous areas of Iraqi Kurdistan emigrated to Israel, and, during the next few years, a number of them settled together in Kfar A, a small cooperative farming community ('moshav') in the Judean Hills, about 45 km south-west of Jerusalem. The surviving settlers and their adult (more than 25 years of age) descendants now number about 250, about 180 of whom presently reside in the community, divided among 81 households.

Upon arrival in Israel, the immigrants were temporarily housed in a reception centre, at which a number of medical procedures, including examination of the skin for the presence of lesions suggesting leprosy, were carried out. The immigrants suspected of having leprosy were subsequently examined by a dermatologist, lesions were biopsied, and the diagnosis of leprosy was confirmed or denied on the basis of histopathologic evidence. Among the immigrants who settled in Kfar A, 12 cases of leprosy were detected. Two additional leprosy patients were later recognized among the original settlers. In Table 1, the 14 patients are listed, together with the year of birth, year of diagnosis and type of leprosy, all obtained from the Leprosy Register of the Ministry of Health of the State of Israel. Patients were classified largely according to the Madrid classification. An additional class – non-characteristic – was also employed.

Table 1. Leprosy patients in Kfar A

Patient	Sex	Year of birth	Year of diagnosis	Type[a]
1. AMO	M	1915	1951	L
2. ANA	F	1937	1951	I
3. AYO	M	1943	1951	I
4. DDT	F	1945	1952	L
5. DEL	M	1932	1952	N
6. DES	F	1947	1952	T
7. DME	M	1943	1952	I
8. DMI	M	1943	1952	I
9. DNA	F	1941	1952	L
10. DPI	M	1936	1952	L
11. MDA	M	1941	1952	N
12. MKR	F	1925	1952	L
13. MYA	M	1919	1963	I
14. YSH	M	1888	1967	I

[a] L = Lepromatous; I = indeterminate; T = tuberculoid; N = 'non-characteristic'.

Since settling in Kfar A, the families from the four areas of Kurdistan have come to be divided among four clans, according to the specific area of origin and family ties. The four clans are here designated as the B, C, D and E clans. The B clan is the largest, including approximately 40% of the adult population of Kfar A.

Interviews were conducted among the adult population of the community, as a result of which all of the adult members of the community were identified; extensive inquiry was made into family relationships; the residence history of every adult was recorded; and pre-existing kinship charts of the four clans were corrected and extended into earlier generations. The 14 leprosy patients were located on the kinship charts, and an analysis of the distribution of leprosy patients was carried out.

All sibships were tabulated according to clan, size of the sibship and the presence within the sibship of patients with leprosy. To analyse statistically the distribution of the leprosy patients among the sibships, the frequency distribution of sibship size was determined. Assuming the patients to be distributed randomly among the sibships, the conditional distribution of the number of patients for each size of sibship was taken to be the binomial distribution, employing the prevalence of the disease in the total population of siblings. The conditional probabilities, together with the relative frequency of sibships of every size, were used to calculate the unconditional probabilities for every possible number of patients in a sibship. Multiplying the unconditional probabilities by the total number of sibships yielded the expected number of sibships containing every number of patients. The observed distribution of patients among sibships was compared with the expected distribution by means of the χ^2 goodness-of-fit test.

Results

Twelve of the 14 patients with leprosy were found to be members of only four sibships, all belonging to the B clan; the remaining two patients, without sibs, were also members of this clan. In addition, as shown in Fig. 1, one patient, who died in an Iraqi leprosarium, and two individuals suspected of having had leprosy, who had died in Iraq, were also members of the B clan. The two suspected leprosy patients were considered as non-patients for the purpose of this analysis.

Ninety sibships composed entirely of members above the age of 25 years were available for analysis. All of these sibships were represented in Kfar A, but many included members who had died, either in Iraq or in Israel, or who no longer resided at Kfar A. As shown in Table 2, these 90 sibships included 407 individuals, of whom 13 were leprosy patients, yielding a prevalence of

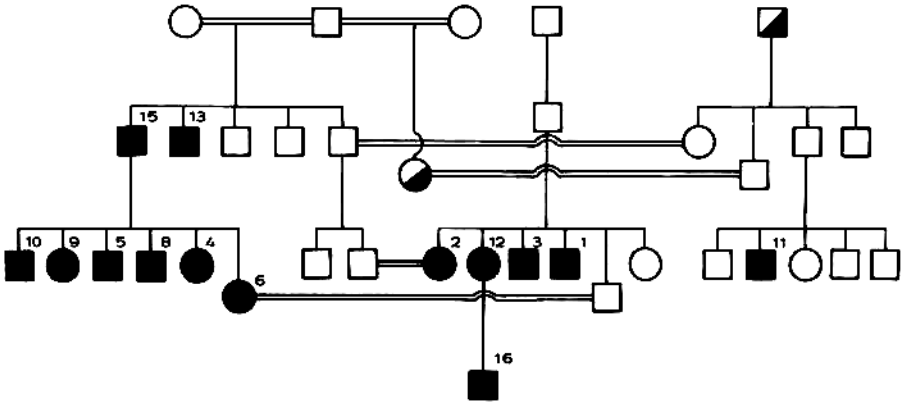

Figure 1. Simplified pedigree of a portion of the B clan, showing the patients with leprosy. Simplification was achieved by omitting those female members who were not leprosy patients, members of sibships containing leprosy patients, heads of households, or needed to demonstrate connections through marriage among the families that included leprosy patients. Fully shaded symbols represent leprosy patients whose diagnosis is not in doubt; the patients are numbered to correspond with those listed in Table 1. Patient No. 15, not included in Table 1, died in an Iraqi leprosarium. Patient No. 16, also not included in Table 1, was not included in the study because he was born in Israel within the last 25 years. The partially shaded symbols represent those suspected of leprosy in Kurdistan.

Table 2. Distribution of leprosy patients among sibships in Kfar A

	No. of sibships with indicated no. of cases									
Size of sibship	No. of cases 0	1	2	3	4	5	6	No. sibships	No. cases	No. people
2	15	0	0	–	–	–	–	15	0	30
3	20	0	0	0	–	–	–	20	0	60
4	16	0	0	0	0	–	–	16	0	64
5	11	1	1	0	0	0	–	13	3	65
6	11	0	0	0	1	0	1	13	10	78
7	5	0	0	0	0	0	0	5	0	35
8	2	0	0	0	0	0	0	2	0	16
9	2	0	0	0	0	0	0	2	0	18
10	3	0	0	0	0	0	0	3	0	30
11	1	0	0	0	0	0	0	1	0	11
Total	86	1	1	0	1	0	1	90	13	407

No. cases per sibship	No. siblings Expected	Observed
0	77.89	86
1	11.49	1[a]
⩾2	0.62	3[a]

$\chi^2 = 5.52$

$\chi^2_{P=0.95,\ 1df} = 3.84$

$\chi^2_{P=0.99,\ 1df} = 6.64$

[a] Pooled for calculation of χ^2

3.2 per 100. All 13 patients were members of four sibships that included 22 sibs. As shown in the lower panel of Table 2, the number of sibships of all sizes with no patients was significantly greater than that expected, and the number of sibships with at least one patient was significantly smaller than that expected, if the patients had been randomly distributed among the 90 sibships ($0.05<P<0.01$).

The B clan included 38 sibships, which were composed of 169 individuals, of whom 13 were patients with leprosy (prevalence = 7.7 per 100). Also in the B clan taken separately, the numbers of sibships with no patients and those with at least one patient were significantly different from those expected if the leprosy patients were randomly distributed among the sibships of the B clan ($\chi^2 = 6.67, P<0.01$).

Discussion

The study of the intrafamilial distribution of leprosy patients is subject to errors and biases that derive from several sources.[3] Complete ascertainment of the status of each member of the family, whether healthy or a leprosy patient, is often difficult if not impossible. Family members may have left the family home, and the status of their health may not be easily determined. Affected members may be concealed. And, especially in retrospective studies, unaffected members of the family may simply have been forgotten.

The possibility that the results of the study in Kfar A may have been influenced by ascertainment bias appears small. Emigration from Kurdistan to Israel does not appear to have been selective. Rather, the Jewish population of Iraqi Kurdistan emigrated *en masse* to Israel. There was simply no opportunity to examine prospective immigrants in advance of their arrival in Israel, and to exclude those suffering from certain diseases. To the contrary, one patient – AMO, who was found to have leprosy in Baghdad, which served as a way-station for Kurdish Jews emigrating to Israel, and was then hospitalized in an Iraqi leprosarium – was brought from the leprosarium to Baghdad in order to rejoin his family in the final days before leaving for Israel. Another patient (No. 15 in Fig. 1) died in the Iraqi leprosarium during patient AMO's stay there.

Analysis of family data may also be difficult.[3] Definitions of 'family' vary from study to study, and an individual may belong to more than one family. Corrections for age and family size are also difficult. Younger members may still be in the incubation period. And the larger the family, the greater the likelihood that it will include more than a single patient. The data derived from the study of the kinships in Kfar A appear to be free of these difficulties. Most of the individuals included in the kinship charts of Kfar A are alive; our inquiry was designed specifically for the purpose of providing kinship data; and it was possible by repeated questioning of the same and different members of the

community to resolve points in dispute. Finally, sibships are non-overlapping; an individual can belong only to one.

Beiguelman[4,5] studied the distribution of leprosy cases among sibships in an area of Sao Paulo State, Brazil, and, in fact, employed the same mathematical approach used in this paper. However, because the study was restricted to affected sibships, he was unable to derive an estimate of prevalence from his data. Therefore, Beiguelman could demonstrate only that his data were inconsistent with intrafamilial clustering of leprosy cases if leprosy prevalence were very high (80–100 per 1,000), a very unlikely figure, but were entirely consistent with intrafamilial clustering if the prevalence were as low as 3 per 1,000, an estimate based on other data available to him.

Review of the literature has revealed only two articles in which are presented large kinships including unaffected as well as affected sibships, that can be subjected to analysis of the frequency of leprosy cases in sibships, as we have done with the data from Kfar A. The first[6] presented a large kinship, constructed from the records of a leprosarium in New Brunswick, Canada, which included 157 siblings, among whom were 78 patients with leprosy. Analysis of the sibships of this kinship demonstrates familial clustering of the leprosy patients ($\chi^2 = 13.00$, $P<0.01$). The second[7] presented a somewhat smaller kinship constructed from the records of the Public Health Service Hospital, Carville, Louisiana. This kinship included 41 people, among them 16 patients, distributed among 13 sibships. Familial clustering of the leprosy patients of this kinship is only suggested by these data. Interpretation of the data from these two studies requires some caution. One cannot assess the completeness of the information presented in the two kinship charts. One may well suspect them of inaccuracies, however, based as they are on the retrospective study of information that had undoubtedly been assembled for another purpose.

Having established familial clustering of the leprosy patients of Kfar A, of what significance is this finding? The two published studies[1,2] of the familial distribution of leprosy patients were carried out in areas of relatively high prevalence, in which opportunities for infection by *Mycobacterium leprae* are not restricted to the family. But as has already been shown, multi-case families accounted for only a small minority of leprosy patients in the two areas studied. In Kfar A, on the other hand, the sources of *M. leprae* infection appear to have been limited both in time and number. Responsibility for case follow-up as well as for case-finding is centralized in the Ministry of Health, and all patients are seen in a single, free, Ministry-operated clinic in Jerusalem. Because they were brought under treatment as soon as they were detected, it appears likely that most of the infectious patients in Kfar A were rendered non-infectious by treatment as early as 30 years ago. The prevalence of leprosy in Israel is smaller than 0.1 per 1,000 (fewer than 250 living registered patients in a population greater than 2,500,000); thus, source-cases are few indeed, and the risk of

infection by *M. leprae* must be limited to those in close (household) contact with one of the few infectious patients. In fact, the one leprosy patient among the Israeli-born members of the community detected thus far (patient No. 16 in Fig. 1) is the son of one of the 14 patients.

As a consequence, both in Israel and in other developed countries into which leprosy patients have immigrated, it appears justified to restrict case-finding activities to the members of the affected families. In addition, it now appears possible to consider a programme of targeted chemoprophylaxis. Programmes of chemoprophylaxis employing dapsone or acedapsone may be too expensive to be considered in developing countries in which leprosy is endemic. The cost of such programmes in a developed country is not great, however, especially if the chemoprophylaxis can be limited to those most at risk of developing the disease. In Kfar A, chemoprophylaxis could be limited to members of the B clan, and even more narrowly to those of the B clan whose residence history includes residence with a leprosy patient.

Acknowledgement

This work was supported in part by the Immunology of Leprosy (IMMLEP) component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, and by the Leprosy Unit of the World Health Organization.

References

1 Noordeen SK, Mohamed Ali P. A study of 579 families having multiple cases of leprosy. *Lepr India*, 1964; **36**: 176–81.

2 Sharma VK. The epidemiologic significance of leprosy within the household. *Int J Lepr*, 1968; **36**: 1–16.

3 Fine PEM. Immunogenetics of susceptibility to leprosy, tuberculosis and leishmaniasis: an epidemiological perspective. *Int J Lepr*, 1981; **49**, 437–54.

4 Beiguelman B, Dall'Aglio FF, Da Silva E. Analise de recorrencia familial de lepra. *Rev Paul Med*, 1968; **72**: 105–10.

5 Beiguelman B. An appraisal of genetic studies on leprosy. *Acta Genet Med Gemellol*, 1972; **21**: 21–52.

6 Aycock WL, McKinley EB. The roles of family susceptibility and contagion in the epidemiology of leprosy. *Int J Lepr*, 1938; **6**: 169–84.

7 Aycock WL. Family susceptibility as a factor in the propagation of leprosy in North America. *Int J Lepr*, 1940; **8**: 137–50.

Lepr Rev (1982) **53**, 285–296

An Urban community's thoughts about leprosy: a survey in Guyana

ANNE COOK
Department of Sociology, Faculty of Social Sciences, The University of Guyana, Box 101110, Georgetown, Guyana

Received for publication 11 September 1980

Introduction

The study was prompted by the need to provide a basis for community education work by personnel attached to the Hansen's disease unit of the Georgetown Public Hospital, Guyana. The importance of understanding what attitudes prevail in a community before starting an educational campaign, especially when the subject of the campaign is a disease or condition carrying a stigma, has been proved many times; when dealing with conditions which arouse irrational fears, educators run the risk of increasing rather than reducing anxieties and prejudices if they enter the field ignorant of the community's feelings and beliefs.

A questionnaire survey was considered to be the best method of approach, for although surveys cannot provide the detailed and rich information of in-depth interviews, they allow for the coverage of large populations and for the comparison of different population groups, such as age groups – of particular interest in this study. A problem clearly exists in the interpretation of responses to questionnaires, as there may be a wide gap between what people say in response to a questionnaire and their actual behaviour. Reaction to an actual and particular leprosy patient, for example, may be quite different from reaction to 'leprosy patients' in the abstract. However, whilst the questionnaire may be a poor indicator of individual behaviour, it is often an excellent indicator of stereotypical ideas in a community and consequently of how a community will react to, say, the conversion of a leprosarium into a general hospital, or a domiciliary treatment programme, or an educational campaign.

Following Bijleveld[1] the questionnaire dealt with diseases other than leprosy so that the latter could be viewed in the context of people's thinking about disease in general. As Bijleveld suggests, it is easy to be impressed by the visible horror of advanced leprosy and, we would add, influenced by the long history

0305–7518/82/053285 + 12 $01.00

add, influenced by the long history of leprosy in Western thought as a uniquely stigmatizing malady. This should not, however, lead to an assumption that leprosy holds a unique position in the mind of the community one is investigating.

Method

The area selected for the survey is within Georgetown, the capital. Its population is mixed, with both major ethnic groups and a variety of occupational groups and levels being represented. Response to the survey was good, with few people refusing to be interviewed. In Guyana, as in many Third World countries, there are problems in finding an accurate, up-to-date listing of persons which can serve as a sampling frame, and an alternative method of selection was therefore adopted. The interviewers went to every house in six randomly selected Census Enumeration Districts. They requested the names of all members of each household over the age of 18, and listed them in the order given by the informant, thereby compiling a sampling frame as they proceeded. Interviews were attempted with every fourth person on the list, the list being built up as the interviewers went along. In this way a quasi-random sample was achieved. The interviewers were university students who had studied social science methodology, and in addition they were given training sessions in the use of the questionnaire. Two hundred and sixty-eight interviews were conducted. There were 15 refusals, and 54 persons could not be contacted. There is what would appear to be a bias in the sample in the direction of an over-representation of females, the distribution being 105 males to 164 females. We have the impression, however, that there actually are more women in the area than men, but this is difficult to substantiate, although the census data for the area do indicate a slight preponderance of females. The ethnic groups were represented thus: Afro-Guyanese 115 (43%); Indo-Guyanese 108 (40%); mixed 35 (13%); other 10 (4%). The occupational groups were represented thus: white collar 61 (23%); skilled manual 33 (12%); unskilled manual 39 (15%) and unemployed 135 (50%). Total 268.

Serious diseases

We started by finding out what diseases came to the minds of the respondents when asked to give the four they considered most serious. In all, 53 distinct conditions were named, although this number included some vague categories like 'belly pain' and 'joints ache'.

The answers to this and other questions were analysed using age as a variable. The sample was divided into those under 30 and those over. As can be seen from Table 1 leprosy was mentioned spontaneously as a serious disease by 11%

Table 1. Seven diseases considered 'most serious'

	Under 30s		Over 30s		Total*	
	No.	%	No.	%	No.	%
Cancer	61	52	84	56	145	54
Tuberculosis	41	35	63	42	104	39
Venereal disease	37	32	42	28	79	29
Typhoid	30	26	42	23	72	27
Diabetes	30	26	37	24	67	25
Malaria	22	19	27	18	49	18
Gastro-enteritis	21	18	28	18	49	18
Leprosy	14	12	16	11	30	11

*All other diseases were mentioned 35 times or less.

of the respondents as compared with cancer, mentioned by 54%. This, taken in the light of responses to later questions, suggests not that leprosy is considered a mild disease, but rather that it is not a disease which is uppermost in the minds of most people. An additional hypothesis is indicated by the relative infrequency with which two other stigmatizing conditions – madness (13: 5%) and epilepsy (4: 1%) are mentioned. Leprosy, madness, and epilepsy are all what might be termed 'biblical' diseases, and whilst it may be only a minority who believe they are afflictions sent by God, this notion has influenced the way in which they are viewed by many more.

The respondents were asked to give reasons for their suggestions. This allows for deductions to be made about what constitutes 'seriousness' in a disease for them. Some of the reasons given are: *Cancer*: Neither a cure nor the cause can be determined. No cure. It ends up killing you. It's very rarely cured. It eats your inside away. It can only be diagnosed. *TB*: It's a dangerous disease. There's no cure. It's catching. The victims suffer in a dirty way. You have to be isolated. It's dirty to be coughing and spitting. It results in death. *VD*: Destroys one's health. Deteriorates one's internal system. It can be contagious. It can kill. It stinks up your inside. You will have to be isolated, leads to blood corruption and children sickness. Loss in private parts. Patient's smell offensive. Causes mental disorder and blindness. *Diabetes*: Incurable. It's always with you. Serious to life, sucks your blood and eats you away. You have to restrain your diet. It bothers you a long time. You have to use insulin for ever. *Typhoid*: Small children tend to catch the disease easily. Can kill. Makes people wither up and die. Leaves you bald. It leaves you flighty. It is an epidemic. *Malaria*: It's caused by using dirty things. Causes pain in the body. Causes lightness of the brain. It's easily caught. Mosquitoes are always present and your chances of getting it are high. It can cause death. *Gastro-enteritis*: It's very common. Can cause death within hours. It leads to steady vomiting. It kills a lot of children. Children get it very easily. It kills instantaneously. *Leprosy*: It is infectious and

has no cure. People scorn you. It's a shameful disease. The only cure comes from the Maker. It leaves you deformed. Because persons have to be isolated. Because there is no cure for it and it eats your flesh and fingernails. It disfigures you. People would not like to have dealings with you.

After the respondents had given their unrestricted views on serious illness, they were asked to choose the four they regarded as most serious from a list of seven presented to them, one of which was leprosy. The other diseases presented (malaria, tuberculosis (TB), diabetes, venereal disease (VD), madness, epilepsy) were offered on the supposition that they would be considered of a seriousness comparable to that of leprosy, and in the case of VD, madness and epilepsy they were, like leprosy, stigmatizing.

Table 2. Frequency of selection as one of four most serious illnesses

	Under 30s		Over 30s		Total*	
	No.	%	No.	%	No.	%
Venereal disease	99	84	99	66	198	74
Tuberculosis	85	73	109	72	194	72
Diabetes	86	73	78	52	164	61
Leprosy	53	45	88	58	142	53
Madness	65	55	71	47	136	51
Epilepsy	41	35	48	32	89	33
Malaria	35	30	48	32	83	31

*Some respondents selected less than four illnesses.

As can be seen from Table 2, leprosy ranked fourth in the number of selections as one of four 'most serious' diseases. Venereal disease, tuberculosis and diabetes were selected more often, with madness ranking a close fifth. Again the data were analysed by age. Older people were more likely to mention leprosy than younger ones, but the difference was not marked. Venereal disease and diabetes were selected more often by younger respondents. Finally, respondents were asked to name the most serious of the seven listed diseases. Here again VD was most often selected, and whilst leprosy ranked second here, madness and diabetes were selected almost as often. Age differences were not marked, but again, older people were more likely to select leprosy than younger ones (Table 3).

It is clear from these responses that leprosy does not come readily to the minds of many when thinking about illness, but when it has been suggested to them people regard it as a serious and fearful disease. This was especially true for many of the older members of our sample. We proffer an explanation for the consistent age difference similar to that suggested by Bijleveld[1] who found a corresponding age difference in his African sample: for young Guyanese, leprosy may not be a 'present day' disease which can affect them. Many of the older people's awareness of leprosy may have been heightened by a

Table 3. Disease selected as 'most serious' from a list of seven

	Under 30s		Over 30s		Total	
	No.	%	No.	%	No.	%
Venereal disease	39	33	47	31	86	32
Leprosy	16	14	33	22	51	19
Diabetes	25	21	19	13	44	16
Madness	20	17	23	15	43	16
Tuberculosis	14	11	19	13	32	12
Malaria	2	2	6	4	8	3
Epilepsy	2	2	4	2	6	2
Total	117	100	151	100	268	100

youth spent in rural areas where communal ties were close and, leprosy was difficult to conceal and deformity common.

For both age groups the disease most often mentioned as serious was venereal disease. This is, at first sight, a little puzzling since venereal disease is seldom detectable by others from outward appearance and is seldom fatal. To understand why venereal disease figures so prominently, we have first to consider that it has been, and is, a relatively common complaint in Guyana. Next we must look at the reasons given for selecting any of the seven diseases as 'most serious', in order to see what constitutes 'seriousness' for the respondents. In connection with the seven designated diseases, the non-existence of a cure was mentioned most often (by 87 respondents), followed by contagiousness (51 respondents), fatality (36 respondents) and deformity and spoiling of appearance (25 respondents).

As would be expected, these four factors were not applied with equal frequency to all the listed diseases. Diabetes, for example, was overwhelmingly spoken of as a disease with no cure, whilst tuberculosis was most often regarded as serious because of its contagious nature. Venereal disease was also deemed serious most often because of the danger of contagion associated with it. Leprosy was most often thought of as serious because of incurability – by 25 respondents from a total of 51 selecting leprosy. Noticeable in the case of both venereal disease and leprosy, however, was the spread of responses. Those two diseases tap several sources of anxiety and whilst many respondents saw neither of them as fatal, both were considered dirty, shameful, destructive of the body and difficult or impossible to cure.

When we turn to the responses to the question 'Which of these diseases would you be most afraid of getting?' again we find leprosy and venereal disease most often selected. This time, however, they are joined by another stigmatizing condition, madness. Young respondents named madness more often than older ones, with the latter choosing tuberculosis and to a lesser extent leprosy more often than the 'under thirties'. It is difficult to find an explanation for the

Table 4. Diseases respondents fear

	Under 30s		Over 30s		Total*	
	No.	%	No.	%	No.	%
Venereal disease	33	28	47	31	80	30
Leprosy	31	27	48	32	79	29
Madness	44	38	29	19	73	27
Diabetes	26	22	27	18	53	20
Tuberculosis	19	7	34	22	53	20
Epilepsy	9	8	14	9	23	9
Malaria	6	5	5	3	11	4
All	7	6	15	10	22	8
None	2	1	1	5	3	1

*Some respondents mentioned more than one disease.

greater preoccupation of young people with madness, but that older ones should mention tuberculosis more frequently is undoubtedly due to the memories some have of the disease as a common scourge. As with the reasons given for regarding leprosy as serious, a variety of causes for fearing it are named. Cancer is frightening because it kills – leprosy for many reasons.

Curability and fatality

As will be seen later, venereal disease and leprosy share another similarity; they are both considered by many to be 'shaming'. For many of our respondents, however, these two diseases are quite different in their prognosis.

Only 18 people (7%) felt that venereal disease was never curable whilst over half (161: 61%) indicated that leprosy could never be cured. Leprosy is seen as a process of progressive deterioration, especially of the *outward* appearance, which for most respondents did not resolve itself in death. Conversely, while

Table 5. Perception of the curability of listed diseases

	Always curable		Sometimes curable		Never curable		Don't know		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Tuberculosis	70	26	167	63	25	9	6	2	268	100
Malaria	135	50	117	44	8	3	8	3	268	100
Venereal disease	90	34	148	55	18	7	12	4	268	100
Madness	35	13	113	42	118	44	2	1	268	100
Diabetes	31	12	92	34	133	50	12	4	268	100
Epilepsy	26	8	106	40	117	44	19	8	268	100
Leprosy	20	7	71	26	161	60	16	7	268	100

venereal disease was thought by most to be usually curable it often led to death after the deterioration of the *inner* organs.*

The Guyanese, like the Bawanga studied by Bjiveveld, appear to take a pessimistic view of illness. The majority of respondents felt that *all* of the diseases mentioned, with the exception of leprosy, led to death. It is worth pointing out here that the interviewers were instructed to stress the word 'usually' in asking the question 'Do you think any of these diseases usually kill people?' Leprosy was the disease least often thought of as fatal yet most often deemed incurable. In this respect it resembles madness most closely. So although the questionnaire did not allow for the deeper probing of this issue, it is clear that for our sample madness and leprosy are chronic ailments *par excellence*, not usually leading to death but condemning the patient to a lifetime of illness.

Table 6. Perception of the fatality of listed diseases

	Usually kills		Does not usually kill		Don't know		Total	
	No.	%	No.	%	No.	%	No.	%
Tuberculosis	195	73	56	21	17	6	268	100
Malaria	171	64	66	25	31	11	268	100
Venereal disease	142	53	93	35	33	12	268	100
Madness	115	43	122	46	31	11	268	100
Diabetes	230	86	31	12	7	2	268	100
Epilepsy	206	77	46	17	16	6	268	100
Leprosy	86	32	123	46	59	22	268	100

The recognition of symptoms

It was considered important to find out what people recognized as symptoms of leprosy, so that officers concerned with public education could have an idea of what imagery of leprosy is prevalent. Few people when asked 'Do you know of any ways to tell if someone has leprosy' gave detailed answers and a substantial proportion (85: 31%) gave a negative reply. Even fewer (4) discriminated between types of leprosy, those that did using the terms 'wet and dry' leprosy.

Skin abnormalities, excluding sores, were mentioned most often (115: 43%) with 65 people giving no other means of recognition. This is a wide category including several types of skin condition. Some examples of responses placed in this category are: 'The skin gets raw looking. It loses its pigmentation and gets scaly. The skin starts to peel. The skin gets white spots. The skin changes colour. The skin deteriorates. If it's in your blood a rash appears seasonally.' The most common suggestion regarding skin abnormalities was that leprosy can be recognized by the appearance of white spots or a loss of pigmentation.

*It is of interest that several respondents indicated that VD 'leads to' syphilis as it becomes worse.

Now a whole range of ailments involve skin changes, many of them mild, like allergy rashes, teenage pimples and fungal infections. Grave illnesses that we are frightened of may be all the more threatening when their initial symptoms seem innocuous – a cough, a slight chest pain or whitish patches on the skin – and easily confused with other conditions. Sixty-three respondents (23%) spoke of deformities usually those involving the hands and, less often, the feet. A typical suggestion was that fingers become 'drawn up' or 'crumped'. Very few (15) referred to a loss of the extremities and even fewer (7) to anaesthesia, or loss of sensation (Table 7).

Table 7. The symptoms of leprosy

	Under 30		Over 30		Total	
	No.	%	No.	%	No.	%
Skin	54	46	61	40	115	43
Deformity	25	21	38	25	63	23
Loss of extremities	4	3	11	7	15	6
Sores	8	7	6	4	14	5
Flesh nodules	4	3	7	5	11	4
Anaesthesia	2	1	5	3	7	3
Don't know	41	35	44	29	85	31
Other	6	5	13	9	19	7

This finding must be interpreted cautiously since Guyanese have comparatively little experience of being interviewed and consequently have not acquired the 'social meaning' of the social research questionnaire. Consequently they often respond to questions of opinion as if they were questions of fact. The interviewers report that respondents, after giving their views on, say, which are the most serious illnesses, would ask if their reply was correct. The apparent ignorance of a significant proportion of our sample about symptoms may in many cases reflect a reluctance to hazard an answer about which they are uncertain in case it is 'incorrect', rather than a complete absence of ideas on the subject.

Shame, scorn and disease

When asked to name those diseases of the seven that were considered 'shaming', respondents of both age groups overwhelmingly specified venereal disease and leprosy. Seventy-two per cent said that they would not let others know if they had leprosy. An examination of the reasons given for a disease being shaming suggests that responses fall into three basic categories: a disease is shaming because of its cause, the discreditable symptoms it has, and the reaction of others to those who have it. The shame associated with venereal disease is because of its sexual associations. Guyanese are not puritanical in their approach

to sexuality and yet there is a reticence about its public display and discussion. A person publicly known to be a venereal disease sufferer offends this reticence.

The shame associated with leprosy and venereal disease contributes to a reluctance to seek treatment with qualified doctors or at public clinics. People with VD may attempt treatment themselves or with 'traditional' healers rather than risk being seen to enter a social disease clinic. Concealment of leprosy or venereal disease obviously poses a threat to the early diagnosis and treatment of these diseases in Guyana.

Educational programmes alone tend to have limited success in changing entrenched attitudes. Attempts to persuade the public that a disease is not shameful when people are quite convinced that it is, simply do not work. This attitude may be strengthened in some countries by poor facilities for the treatment of venereal disease, leprosy and insanity, together with punitive legislation against those afflicted.

In Guyana, the bright new clinic for the treatment of skin disorders will probably have more effect than mere words in convincing people that leprosy should be regarded as an illness requiring prompt treatment like any other, rather than a curse which leads inevitably to shameful degeneration and isolation from society.

Willingness to associate

Respondents were asked to indicate their willingness or otherwise to associate with a person being treated for leprosy or allow their children to associate, at different levels of intimacy – in a working relationship, a friendship relationship, having a child visit a patient, having a child marry a patient.*

Over half the sample said that they would be willing to work with, or befriend a patient. This figure must be interpreted cautiously for friendliness and tolerance are important social values for Guyanese, and the reaction of

Table 8. Willingness to associate

	Yes		No		Don't know		Total	
	No.	%	No.	%	No.	%	No.	%
Would work at same place	145	54	109	41	14	5	268	100
Would be friends with	156	58	98	37	14	5	268	100
Would allow child to visit	113	42	128	48	27	10	268	100
Would allow child to marry	16	6	215	80	37	14	268	100

*The questions were centred on the phrase 'a person being treated for leprosy' rather than 'a person with leprosy' or even 'a leprosy patient' as the intention was to test people's reaction to persons who are non-infectious, thus isolating stigma from fears of infection. This intention was not fulfilled however, as so few people are apparently aware that treatment renders a patient non-infectious.

many to the hypothetical situations put to them may well have been tempered by a desire to give a 'socially acceptable' response. Those who work with leprosy patients can give many examples of the norms attached to these social values breaking down, with the result that patients are repudiated as friends and rejected as fellow-workers. Fewer respondents reacted positively to the idea of having their children mix with patients. The most outstanding finding within this area was that a mere 16 respondents claimed a willingness to allow a son or daughter to marry a patient. Now there were indications that the notion that leprosy is hereditary is not uncommon, but that alone cannot account for this almost unanimous rejection of patients as children's marriage partners. If we remember that leprosy is thought of as a hopeless disease, with no cure and no release through death, it becomes reasonable to feel that patients make poor marriage prospects. Furthermore a family relationship which threatens to taint one with the patient's stigma may be intolerable.

The treatment of leprosy

Our respondents were asked where leprosy should be treated, and were offered a choice of Mahaica Hospital, any other hospital, or domiciliary treatment. The majority (209: 78%) felt that Mahaica Hospital was the place for treatment, although a few of this number (9) saw domiciliary treatment as an alternative (Table 9). In Guyana leprosy is now treated on a domiciliary basis. The specialist hospital at Mahaica houses 'old' patients and is rarely used for new admissions.[2]

Table 9. Choice of treatment

	No.	%
Mahaica Hospital	200	75
Mahaica Hospital or domiciliary	9	3
Any hospital	21	8
Domiciliary	33	12
Don't know	5	2
Total	268	100

The responses suggest that the overwhelming selection of Mahaica probably came about for several reasons. Some people feel that Mahaica is best for the patient as it offers specialist care. Others no doubt made the same choice feeling that the confinement of patients offers society protection from contagion and also from the anxiety and embarrassment which is aroused by social contact with the 'abnormal'. In this connection, it is of interest that 178 (66%) agreed with the statement that 'Leprosy patients should be kept away from other people' even though only 90 (34%) felt that 'It is dangerous to touch a leprosy patient.', which seems to suggest that fear of contagion is not the only, nor even perhaps the main reason for the rejection of leprosy patients.

Respondents had few suggestions to offer regarding the treatment and cure of leprosy. Most (181: 67%) said they didn't know how this could be accomplished, to which number must be added a further 52 respondents (19%) who mentioned a place of treatment – Mahaica, a clinic, 'at the doctor's' – rather than a method. Of this 52 many stated that leprosy could be treated but not cured, which perhaps explains the recurrence of the phrase '*only* at Mahaica' in these answers, the implications being that the specialist hospital is the only place where anything much can be done, and this falling short of actual cure. Seven people spoke vaguely of injections, drugs, or medicine, four of prayer, two of the efficacy of 'bush' – herbal remedies – and one that of marijuana. Only two mentioned a *specific* treatment; one dapsone, the other sulphur. The area of treatment seems to be where educational programmes could focus most effectively. If people can be assured that leprosy can be treated and contained then this should reduce the fatalism with which it is viewed, and this in turn improve attitudes towards patients and decrease the incidence of 'hiding' and defaulting on treatment.

The prevention of leprosy

There was a greater abundance of ideas as to how leprosy could be prevented. The preventive measure most often recommended was to simply keep away from people with the disease. Others mentioned cleanliness, the avoidance of certain foods, making regular checks with a doctor and the use of marijuana. Most (163: 61%) could make no suggestions.

It is notable, however, that 49 (18%) respondents agreed with the statement 'Some foods give you leprosy.', and a further 123 (46%) showed uncertainty, stating that they did not know if this was so. Also 48 (18%) agreed that leprosy could be contracted if obeah (supernatural arts) were used against one, although 161 (60%) disagreed, with 59 (22%) being uncertain.

It can be concluded then, that folk ideas about the prevention and cure of leprosy persist in this urban community. Only two respondents recommended folk methods of treatment for leprosy, however, and it seems accepted that the appropriate treatment of leprosy is offered by qualified doctors.

Conclusions

Leprosy is regarded as a serious and fearful disease by urban Guyanese. This does not appear to be a function only of the characteristics of the disease but results from a perception of leprosy as stigmatizing. A vicious circle is thereby created: people 'scorn' leprosy because of the stigma attached and the stigma is attached to leprosy because people 'scorn' it. Thus leprosy belongs to that group of diseases that 'discredit' their victims. What makes leprosy particularly

frightening, especially for older people, is the prevalent notion that it is incurable, yet not fatal. At this point we would mention the fact that during the course of the interviews not a single respondent indicated a knowledge of the fact that treatment renders a patient non-infectious. The treatability of leprosy is the point which can be stressed most profitably in education programmes. It seems reasonable to expect that once the view of leprosy as untreatable is corrected, then fears about contagion may be more easily allayed, domiciliary treatment may be more acceptable, and gradually the stigma may begin to fade. This would seem to be the area where education is most needed and where there is most chance of effecting a break in the 'vicious circle' of stigma.

Younger people, as a group, seem less aware of, and less afraid of, leprosy. Perhaps health programmes addressed to them in schools and universities can capitalize on this and emphasize the treatment of leprosy along with that of other diseases.

Acknowledgement

The survey was generously funded by the American Leprosy Missions, Inc.

References

[1] Bijleveld I. *Leprosy and other diseases in the three wangas: community thought patterns about health care and their consequence for emergent patients.* Royal Tropical Institute, Amsterdam, 1976.

[2] McDougall A C, Rose P. Integrated leprosy control in Guyana. *Bull Pan Am Hlth Org* 1978; **12**: 11–6.

Lepr Rev (1982) **53**, 297–305

SPECIAL ARTICLE

Integration of leprosy into general health services in an urban area – a feasibility study *

C R REVANKAR[†], SAROJ S JHA[‡], V V DONGRE[§], S S DESHPANDE[†] & R GANAPATI[†]

[†]*Bombay Leprosy Project, 6/27 Amar Bhuvan, Sion-East, Bombay–400 022, India;* [‡]*Preventive and Social Medicine Department, Topiwala National Medical College, Bombay–400 008, India;* [§]*R.R.E. Society, Acworth Leprosy Hospital, Wadala, Bombay–400 031, India*

Received for publication 1 March 1982

Summary To study the feasibility of integrating leprosy treatment into the general health services in Bombay, 198 doctors (essentially private medical practitioners), 120 interns, 32 nurses and 126 other auxiliary health staff were involved in intensive orientation programmes of various types, and doctors were offered a free consultative service and guidance, with a free supply of dapsone. They were encouraged to treat leprosy patients in their own set-up without referring them elsewhere.

After 18 months' follow-up, it was found that 108 doctors (59%) suspected 771 leprosy cases, of which 724 (94%) were labelled as leprosy. The investigators confirmed personally 129 of 158 (82%) which were seen by these doctors: 70% were of tuberculoid type, 6% were lepromatous and 22% borderline type. Out of 50 whose skin smears could be taken 25 (50%) were positive for AFB. At the end of scheme, it was found that 42% of all cases were under regular treatment.

Short-term follow-up assessment showed that 58% of doctors treated cases in their clinics as compared to 8% before study. Similarly the percentage of doctors who referred cases to leprosy clinics or dermatologists was reduced to 42%. Ninety-two per cent of patients expressed their desire to continue treatment from their doctors only. It is concluded that if proper diagnostic guidance and encouragement is given, doctors may be able to manage uncomplicated leprosy cases. Integration is feasible in the urban situation so that leprosy patients get the benefit of health care at the level of 'first contact' with the peripheral service.

Introduction

Health care in Bombay is organized by public as well as private health units. In public sectors such as municipal services, in addition to medical staff, paramedical staff – nurses, health

*This project was supported under grant-in-aid from the Indian Council of Medical Research, New Delhi, India.

0305–7518/82/053297 + 09 $01.00

visitors and medico-social workers – play a very important role. It is the general medical practitioners and specialists who form the private health system. At a most peripheral level of the urban community, the municipal dispensary, doctors and general practitioners and other health staff deliver basic health services of a curative type at a fairly low cost. It is believed that about 60% of the population in Bombay is cared for by general medical practitioners and that the remainder are dependent on municipal and government systems.

The existing specialized centres for leprosy in Bombay exclusively provide a leprosy service where patients with various difficulties related to their socioeconomic conditions, transport and job problems etc. cannot make full use of such services. A report from the urban areas shows that only 13.1% of patients registered in urban treatment centres were regular and 86.9% dropped out.[1]

For urban leprosy control work, it has been recommended that involvement of general medical practitioners and municipal doctors is essential.[2] However, until recently no such attempt has been made in this direction. The possibilities of involving general medical practitioners in leprosy work through an intensive orientation programme in cities has been reported.[3] An encouraging result has been reported with integration of leprosy into polyvalent population surveys at a paramedical level.[4] Such an approach has been favoured by different authors[5,6] and Horst Buchmann has emphasized that the leprosy control services should be an integral part of primary health care programmes in developing countries.[7]

The present study in Bombay was aimed at finding out the feasibility of such an approach at different levels of health staff, especially at general medical practitioner level, to avoid leprosy cases being referred to specialized leprosy centres or specialists for treatment.

Materials and methods

A well-defined municipal ward – M (Chembur) – and adjacent small areas of N ward (Garodia

Table 1. Types of health staff involved

Health units	Doctors	Interns	Nurses	Laboratory technicians	Ward boys, dressers etc.
General medical practitioners	152 (77%)	–	–	–	–
Municipal General Hospital	11	–	21	4	72
Municipal dispensaries and maternity homes	13	–	8	2	35
Central govt health scheme dispensaries	6	–	2	1	10
Urban health centre (medical college)	6	120	1	1	1
Employees State Insurance Scheme centre (ESIS)	10	–	–	–	–
Total staff	198*	120	32	8	118

*21 (11%) belonged to specialist categories such as dermatology, orthopaedic surgery, paediatrics; 37 (19%) were ESIS practitioners. 118 (60%) were practising allopathy. The remainder were specialists of ayurved, homeopathy, unani and other systems of medicine. 93 (47%) (both municipal and private sector) were practising in the slum area. The remainder were in the mid and high economic population area.

Nagar) were adopted as the project area, where the estimated prevalence rate of leprosy was about 10 per 1,000. The following health units offering curative health services in these areas were included in this study: Municipal General Hospital 1; Municipal dispensaries and maternity homes 10; Urban health centre (attached to municipal teaching medical college) 1; Central Government Health Scheme (CGHS) dispensaries 2; Employees State Insurance Scheme (ESIS) centre 1; General medical practitioners including specialists 250.

The health staff involved in this scheme are shown in Table 1. Doctors, especially those practising general medicine, were given prime importance as they play a very crucial role in the urban leprosy control programme.

METHODS

The whole investigation was divided into three phases.

Phase I. Data on initial awareness about leprosy and other existing antileprosy activities were collected by employing a questionnaire technique.

Phase II. All the health staff included in Table 1 were exposed to an intensive orientation programme including refresher courses, group talks with slide shows in the doctors' clinics, individual visits, discussion (including leprosy case demonstrations), and the distribution of various literature such as books, folders, leaflets and posters. Drugs like dapsone, clofazimine and rifampicin were supplied whenever asked for. Doctors were encouraged to treat leprosy

Table 2. Existing leprosy service in different health structures

Health units	Number of doctors: Contacted	Suspecting leprosy cases	Treating cases	Referring cases	Interested in leprosy
Municipal General Hospital	11	3 (27%)	0	3	3
Municipal dispensaries and maternity homes	13	10 (77%)	1	1	1
Urban health centre	6	0	0	0	2
Central govt health scheme dispensaries	6	2 (33%)	0	1	2
Employees State Insurance Scheme centre (ESIS)	10	1 (10%)	0	1†	1
General medical practitioners	152	104 (68%)	8	96	143
Total	198	120 (61%)	9 (8%)	102 (85%)	152 (77%)

*Due to non-availability of dapsone either on the market or in the municipal schedule (DDS supplied exclusively to specialized centres) even a dermatologist of the Municipal General Hospital had to refer cases to leprosy hospitals.

†In accordance with government rules, ESIS doctors have to refer leprosy patients to leprosy hospitals for certificates and treatment.

cases in their own clinics without referring them to specialized leprosy centres or to specialists. During this phase, 3 refresher courses, 45 slide shows with group talks and 180 individual discussions were carried out. Facilities for skin smears (AFB), were extended by the project.

Phase III. A short-term follow-up assessment was done by (a) interviewing staff by both direct and indirect methods through questionnaire, and (b) interviewing available leprosy patients through a questionnaire. This assessment was undertaken to determine the acceptability of these services both to the health staff, especially doctors, and to patients.

Results and discussions

The existing leprosy service in different health units is shown in Table 2.

AWARENESS OF LEPROSY AND THE LEPROSY PROBLEM

The questionnaire study indicated that 39% of doctors of all categories scored more than 50%, showing satisfactory leprosy awareness (score 50% and above was considered as a basis of satisfactory knowledge). The doctors working under urban health centres and CGHS had better knowledge compared to general medical practitioners where, in the latter group, 35 out of 79 (44%) who completed the first questionnaire scored above 50%. Only 23% of the municipal doctors scored above 50%, although, of the interns who had recently passed their degree examination, 79 out of 113 (67%) who answered questions showed evidence of satisfactory awareness. Awareness amongst laboratory technicians was much better than among nurses.

After approximately 18 months' follow-up the questionnaire study showed the following findings.

Table 3. Leprosy case detection by the doctors

Health units	No. who suspected leprosy cases	No. of cases suspected	No. of cases confirmed
General medical practitioners	90	514 (67%)	478 (93%)
Municipal General Hospital	5	141 (18%)	138 (98%)
Municipal dispensaries and maternity homes	6	26 (3%)	22 (85%)
Central govt health scheme dispensaries	3	24 (3%)	23 (96%)
Urban health centre	2	6 (0.7%)	3 (50%)
Employees State Insurance Scheme centre (ESIS)	2	60 (8%)	60 (100%)
Total	108	771 (100%)	724 (94%)

Of 184 doctors who could be followed up, 108 (59%) suspected leprosy in their clinics amongst their clients.

In the Municipal General Hospital and ESIS centres, attending dermatologists confirmed leprosy cases, whereas elsewhere the cases were confirmed either by the investigators or paramedical workers of the scheme or the doctors themselves.

67% of the cases were suspected by general medical practitioners.

Of 158 cases suspected mostly by general practitioners, 132 (83%) were seen personally and confirmed as leprosy by the investigating team. A sample of 54 (39%) of 138 cases already registered for treatment at the Municipal General Hospital were seen and confirmed by this team. This obviously showed that these doctors were quite capable of diagnosing leprosy cases of all types.

70% of patients were of tuberculoid type – especially in general medical practitioners' dispensaries; 6% were of lepromatous type, of which 2% were detected by general practitioners themselves; 22% of patients were of borderline type.

Of 664 patients of all types examined 186 (28%) could be verified by the investigating

Table 4. Treatment and management of leprosy cases in the general dispensaries

Health units	No. of cases confirmed	No. of cases treated in doctors' clinics*	No. of cases referred for treatment			
			Leprosy hospital†	Private specialists	Municipal Hospital	Total
General medical practitioners	478	178 (37%)	115 (24%)	150‡ (31%)	35 (7%)	300 (63%)
Municipal General Hospital	138	138 (100%)	–	–	–	–
Municipal dispensaries and maternity homes	22	5 (23%)	7	–	10 (45%)	17 (77%)
Central govt health scheme dispensaries	23	21 (91%)	2	–	–	2 (9%)
Urban health centre	3	3 (100%)	–	–	–	–
ESIS centre	60	Nil	60 (100%)	–	–	60 (100%)
Total	724	345 (48%)	184 (25%)	150 (20%)	45 (6%)	379 (52%)

*Despite regular visits and encouragement, doctors treated only 48% of the patients in their own clinics.

†25% of the cases were referred to public leprosy hospital. The main reasons for referring 52% of the patients were for treatment and other complications. Under ESIS, all the patients have to be referred to leprosy hospital for certificates and treatment under existing government rules.

‡31% of the patients from the general practitioners' group were referred to private specialists such as dermatologists mainly because their group practises especially in non-slum areas. But the comparative picture showed definite changes regarding case detection, referral and treatment in the clinics before and after study.

team. Among these cases, 4 had plantar ulcers, 6 had grade II hand deformities (clawing) and 2 had grade I hand deformity (WHO grading).

50 patients were subjected to smear examination (lepromatous and borderline types): 25 (50%) were found to be smear positive for AFB; 7 out of 25 (54%) of these cases were attended by general practitioners. (These smears were taken by the paramedical workers of the project.)

Of 70 interns who completed the second questionnaire 46 (65%) said that they detected cases during their field posting. However, further details were not available.

Results of a short-term assessment

The initial and follow-up questionnaire studies of doctors did not show any difference with reference to their knowledge of leprosy and its problems.

Though 120 interns participated in this scheme, only 70 (58%) completed the second questionnaire. No significant difference was observed in their knowledge. The third questionnaire, sent by post (as these interns left college), had replies from only 5 interns (4%) and no additional information could be gathered.

Attractive posters of small size (on leprosy) may be accepted by these doctors. Of 159 doctors 79 (50%) displayed small-size posters announcing 'Treatment available here' in Hindi, but only 11 (7%) of 159 doctors displayed large-size posters.

29 (27%) of 108 doctors, of whom 23 (80%) were general practitioners, maintained the minimum possible records. The records from the Municipal General Hospital were much better than those from general practitioners. The questionnaire data showed that 88 (75%) of 117 doctors felt that records maintenance was important from the point of view of indicating the regularity of treatment. Unfortunately, however, because they were too busy, those who maintained records did not enter the details of drugs used.

In 60 (23%) out of 264 cases correct addresses were recorded, 34% (90/264) addresses were wrong, and 43% (114/264) were not recorded. Proper recording of addresses is essential in urban areas for follow-up cases, a point which was stressed to these doctors.

Though 108 doctors showed their interest either in case detection or treatment, only 20 (19%) were actually touching patients for examination purpose, the remainder being hesitant to handle them physically for fear of infection. Only 12 (13%) doctors out of 108 were not afraid of leprosy infection.

Table 5. Performance of doctors before and after study

Study	No. who suspected cases†	No. who referred cases‡	No. who treated cases§
Before (198 doctors)	120 (60%)	102 (85%)	9 (8%)
After (184 doctors)*	108 (59%)	45 (42%)	63 (58%)

*The remaining 14 were not available for follow-up.

†Despite regular visits, an almost equal number of doctors suspected leprosy cases after the study.

‡Percentage of doctors who referred cases significantly reduced.

§A very high percentage of doctors starting treating leprosy patients in their clinics. This 58% of doctors were really interested in managing cases in their set up. Of 63 who treated cases in their clinics 39 (62%) were practising allopathy.

Table 6. Treatment status of leprosy patients in various clinics*

Health units	Regular†	Irregular	Drop out‡	Total no. of cases treated
General medical practitioners	111 (62%)	5 (3%)	62 (35%)	178 (100%)
Municipal General Hospital	18 (13%)	0	120 (87%)	138 (100%)
Municipal dispensaries and maternity homes	5 (100%)	0	0	5 (100%)
Central govt health scheme dispensaries	10 (48%)	0	11 (52%)	21 (100%)
Urban health centre	0	0	3 (100%)	3 (100%)
Employees State Insurance Scheme centre (ESIS)	0	0	0	0
Total	144 (42%)	5 (1%)	196 (57%)	345 (100%)

*Though the doctors were told about case holding programme, this was not followed.

†42% of the patients were regular for treatment, which was judged on the available records at the doctors' clinics. To test the validity of this data, 23 urine samples were collected randomly on a surprise visit and subjected to estimation of urine dapsone/creatinine ratio in a standard laboratory. Out of these, 19 (83%) samples showed evidence of patients consuming dapsone tablets regularly. This overall rate of 42% is higher than that reported by others from Bombay.[1]

‡The drop-out rate was high amongst the patients attending a municipal hospital. This was mainly due to the non-availability of dapsone either in the clinics or on the market. However, the overall drop-out rate (57%) at the end of 2 years, was not high as compared to other figures reported from Bombay.[1]

Of those doctors initially suspecting cases 59 (55%) were confident of diagnosing and treating cases. However, they did require the help of investigators or specialists for a second opinion before labelling patients as leprosy cases.

63 (58%) of the 108 doctors were practising in slum areas. This showed that a larger number of doctors in slum areas were seeing cases since slums are well-known for their hyperendemicity.

103 (88%) of 117 doctors who completed the second questionnaire felt that leprosy cases could be treated in their clinics.

More than 80% of doctors favoured integration.

82% of interns favoured integration; 63 (98%) of 70 interns who completed the second questionnaire expressed their willingness to treat leprosy cases wherever they practised.

Most of the nurses from the Municipal General Hospital who were involved were transferred to other hospitals, and hence, could not be interviewed.

Of 8 laboratory technicians, 5 (62%) scored more than 50%, compared to initial assessment. Though their knowledge and attitude towards leprosy changed, none of the technicians agreed to take skin smears for AFB due to fear of infection. Two technicians from the Municipal General Hospital, despite repeated discussions and demonstrations, refused to take

skin smears on the grounds of infection, although they routinely handled sputum of patients suffering from pulmonary tuberculosis.

Of 19 dressers and labourers of various municipal dispensaries and the hospital, 16 (84%) agreed to touch the leprosy patients; 10 (53%) did not have objections towards the treatment of such cases in their set-up.

Questionnaire study of 62 patients who could be interviewed showed that 57 of 62 (92%) expressed their willingness to continue their treatment from their family physicians and municipal hospitals for reasons such as short distances for travel, and convenient times.

Only 5 (8%) patients refused to continue treatment as they felt that either they had to pay for treatment or that drugs were not available.

Conclusions

1. This short-term investigation showed that the general duty doctors, especially general medical practitioners, were quite capable of treating leprosy cases, mostly of uncomplicated types, provided proper diagnostic guidance and encouragement was given them. This could provide patients with services closer to their homes, along with other medical problems at a most peripheral level.

2. Skin smear and perhaps biopsy facilities could greatly augment the treatment services at peripheral level.

3. A regular supply of suitable literature and the running of reorientation programmes would help them to keep in touch with recent aspects of leprosy.

4. Free availability of dapsone in the general dispensaries or market is essential to encourage the doctors to treat leprosy cases.

5. Paramedical staff engaged in other control programmes should also be involved in leprosy work.

6. This short-term study showed that integration is feasible in this urban area. Simple tuberculoid cases could be managed very easily by general duty doctors. The remaining cases, where specialized care is essential, could be referred to specialized centres. This approach would bring down both the cost of the programme and the work-load of the specialized centres.

7. A random sample of patients attending different leprosy centres, family physicians or specialists should be interviewed on a large scale to establish – from the standpoint of the patient – how best to 'deliver' leprosy control and attain maximum compliance.

8. Reorientation of medical education at undergraduate medical student level is essential to create an enduring interest in leprosy.

Acknowledgements

The investigators are grateful to the following for their kind co-operation: the Co-ordinating Secretary, German Leprosy Relief Association, Madras; the Dean, Topiwala National Medical College, Bombay; the President, RRE Society, Acworth Leprosy Hospital, Bombay; the Director, Lok Seva Sangam, Bombay; Chembur Medicos Club, Bombay; Indian Medical Association, Chembur Branch, Bombay; I/C of the Municipal General Hospital and dispensaries; and ESIS, CGHS Centres, Damien Foundation, India; WHO; SEARO, New Delhi; Central Health Education Bureau, New Delhi; the Leprosy Mission, England; ALERT; GMLF Wardha; Association National Amici dei Lebbrosi Italy; Dr A G Kulkarni, Department of Preventive and Social Medicine, TNM College, Bombay; Mr P R Dewarkar, Mr B K Rao, Mr N S Shinkar, Mr B R Prasad Rao, and the staff of Bombay Leprosy Project.

References

1 Koticha KK, Nair PRR. Treatment defaulters in leprosy: a retrospective study of 42,000 cases. *Int J Lepr*, 1979; **47**: 50–5.

2 Operational Guide and Guidelines of Assessment of Leprosy Control Work in India. Govt of India Publication, 1969; 61.

3 Nilkanta Rao MS. Assessment of efforts to induce medical practitioners to participate in urban leprosy control programmes. *Lepr Rev*, 1976; **47**: 149–53.

4 Kapoor PL, Joshi GY, Ranade MG, Nilkanta Rao MS, Deodhar NS. Integrated surveys as a tool for early case detection in leprosy control programme. *Lepr in India*, 1976; **48**: 851–60.

5 Schaller KF. Integration of leprosy control into the health centre scheme. *Lepr Rev*, 1969; **40**: 243–8.

6 Antia NH. The people we fail to reach. (Editorial.) *Lepr Rev*, 1977; **47**: 155–7.

7 Buchmann H. Leprosy control services as an integral part of primary health care programmes in developing countries. German Leprosy Relief Association, Wurzburg. W. Germany, 1979; 1–79.

Lepr Rev (1982) **53**, 306–312

SPECIAL ARTICLE

Suppressor cells of mouse and man. What is the evidence that they contribute to the aetiology of the mycobacterioses?

G A W ROOK
Microbiology Department, School of Pathology, Middlesex Hospital Medical School, Riding House Street, London W1P 7LD

Received for publication 26 April 1982

The existence of subpopulations of lymphocytes which decrease rather than increase certain immune responses, was first suggested in 1970.[1] At first this idea faced considerable opposition, but a decade later most immunologists accept 'suppressor' cells as an essential negative feedback mechanism. All other biological pathways are subject to both positive and negative regulation, and there is no reason to suppose that the immune response is any different. Indeed it now seems reasonable to suppose that the immune response has particular need for negative feedback in order to stop uncontrolled proliferation of lymphocytes, excessively vigorous tissue-damaging responses and, perhaps, auto-immune responses.

Thus the 'regulator' or 'suppressor' T-cell is primarily a normal homeostatic mechanism, which accompanies and modulates all normal immune responses. However, if suppressor cells exist, they can presumably go wrong. Then malfunctioning suppressor mechanisms might inappropriately reduce a much needed response to a pathogen such as *Mycobacterium leprae*, or conversely, fail to suppress an inappropriate response. The advent of monoclonal antibodies has allowed rapid progress in delineating the suppressor cell subsets in lymphocyte populations. Three recent reviews have discussed this in relation to mouse[2,3] and man.[4]

Table 1 shows how these new reagents have allowed T-lymphocytes to be divided neatly into two (or three) subpopulations. It was hoped at first that this would make it possible to define the function of individual cells – unfortunately we are rapidly being disillusioned. As Table 1 shows, several different unrelated functions can be found in each subpopulation. The most important fact in the present context is the existence of suppressor cells within both of them. The most often studied in relation to the mycobacterioses, are the TH_2^+, $T5^+$, $T8^+$ (human) or Lyt $2,3^+$ (mouse) suppressors which include cells which, once triggered, will non-specifically suppress *in vitro* proliferative responses or antibody production (e.g. to mitogens). However, more recently defined are Lyt 1^+, 2, 3^- cells which specifically suppress delayed type hypersensitivity responses to several particulate antigens, including sheep and horse erythrocytes and *Leishmania tropica*.[3]

These experiments with *L. tropica*[5] in Balb/c mice are particularly exciting for leprologists, because they constitute the first clearcut demonstration that suppressor cells can be the direct cause of a failed host response to an intracellular parasite, leading to dissemination and death. It should therefore be noted that the suppressor cells involved are Lyt $1^+,2,3^-$, not the commonly studied Lyt $1^-,2,3^+$ type.

The way in which suppressor T-cells operate is complex and there are probably several mechanisms which cannot all be discussed in detail here. A well-studied example involves a Lyt $2,3^+$ cell[6] which secretes a suppressor factor with a molecular weight between 55 and 60 kd, which is antigen-specific and also carries determinants coded by the I-J subregion of

0305–7518/82/053306 + 07 $01.00

Table 1.

	Antigens* expressed on the lymphocyte surface	
	TH_2, T5, T8, (Man) Lyt 2,3, (Mouse)	T4, (Man) Lyt 1, (Mouse)
Helper cells for antibody production	No	Yes
Suppressors of antibody production	Yes	No
Cytotoxic activity	Yes	No
Activation of macrophages via lymphokine release	?	Yes
Mediate delayed swelling reaction in skin	Yes (some viruses and contact sensitizers)	Yes (most antigens including listeria, leishmania and mycobacteria
Suppressor of delayed type hypersensitivity to particulate antigens (leishmania and erythrocytes)	No	Yes
Suppressors of *in vitro* proliferative responses	Yes	No

*These antigens are not alleles and both can be expressed simultaneously.

the Major Histocompatibility Complex (MHC) (the expression of I–J antigens is a characteristic of suppressor cells[2,6]). This factor then 'arms' 'acceptor' cells which, on encountering the relevant antigen, secrete a non-antigen-specific mediator, which suppresses the response by a mechanism which has not yet been elucidated. (This pathway can be considered to be analogous to the 'arming' of mast-cells by antigen-specific molecules (IgE), so that they release non-specific mediators, for example histamine, when they encounter antigen.) We must assume that each stage in this pathway is itself regulated – induction of suppressor cells, release of mediators, availability of 'acceptor' cells, triggering of 'acceptor' cells.

What evidence is there for a role for suppressor cells in the pathogenesis of the mycobacterioses?

It has been known for several years that massive intravenous doses of mycobacteria can induce in mice a state of anergy[7] and an inability to respond to other antigens.[8] Similarly, *in vitro* proliferative responses to antigens or mitogens are lost during the late phase of dissemination which occurs during infection with lethal organisms such as *Mycobacterium ulcerans* or *M. lepraemurium*. Indeed, during this phase the antigens of the infecting organisms may inhibit rather than enhance *in vitro* lymphoproliferation.[9] Two types of suppressor cell have been implicated: the first is a T-cell, and can be found following large intravenous doses of BCG[10], *M. lepraemurium*,[11] or several *M. avium*-like organisms.[10] The Lyt phenotype is not known, but its effects, once triggered, are non-specific, and probably it will turn out to be Lyt $2,3^+$. There is at present no reason to believe that its appearance *causes* the disease to progress (unlike the Lyt 1^+ suppressors in *Leishmania tropica* infections of Balb/c mice[5]) and it seems more likely to be a consequence of dissemination. Thus it is readily induced by BCG, but the animals rapidly recover and the organisms are eliminated. Since we

know that BCG is pathogenic for mice with severe T-cell dysfunction,[12] this observation implies that this type of suppressor T-cell does not cause severe T-cell dysfunction.

The second kind of 'suppressor' cell found in the presence of heavy systemic loads of mycobacteria or mycobacterial products appears to be a macrophage,[11,13,14] associated with a chronic granulomatous response.[15] It is particularly prone to appear in C57Bl/6 mice and is under non-MHC-linked genetic control.[15] Again there is no evidence to implicate this cell as a cause rather than a consequence of susceptibility, though it may be relevant that C57Bl/6 mice are unusually susceptible to intravenous challenge.[16]

A problem with all this work is that no experiments have been performed to demonstrate whether transfer of the suppressor cells to normal recipients will increase their susceptibility to subsequent challenge. Moreover, we do not even know whether the intravenous challenge is relevant to the human mycobacterioses. Dissemination of mycobacterioses occurs, but the route of primary infection is obviously not intravascular.

One author has attempted to avoid both of these objections.[17] Mice (C57Bl/6 and Balb/c) were infected subcutaneously with *Mycobacterium lepraemurium.* It was found that a population of cells developed in the spleens of Balb/c mice (but not C57Bl/6), which, when transferred into irradiated Balb/c recipients, resulted in significantly decreased resistance to *M. lepraemurium.* This observation remains unique, and suggests a relevant type of suppression. Dissemination from subcutaneous infections is common in Balb/c mice, but not in the C57Bl/6 strain. However, the fact that the cell recipients had to be irradiated for the effect of the suppressors to be demonstrable, clearly detracts from its value. Moreover, the cell involved had quite different properties from the suppressor T-cells demonstrated following intravenous challenge (described above) and therefore this experiment does not provide independent support for the relevance of the latter.

Another group has studied the size of the granulomata developed in the tissues of mice following intravenous injections of killed BCG suspended in oil droplets.[18] They have found that some strains (such as C57Bl/6) develop very large granulomata. On the other hand in CBA mice, granuloma formation is rapidly 'switched off' by a suppressor cell population. It may therefore be relevant that C57Bl/6 mice are very good at localizing cutaneous challenges with virulent mycobacteria, whereas in CBA mice dissemination readily occurs. In contrast C57Bl/6 mice are very susceptible to intravenous challenge. Perhaps unsuppressed granuloma formation contributes to localization in the periphery, but also to pathology in deep tissues. This model seems interesting and relevant. It would be helpful to know how these 'granuloma-modulating' suppressor cells are related to those described in other experimental systems above.

The situation is no clearer when we consider man. There are a number of cellular mechanisms which regulate the *in vitro* proliferative responses of peripheral blood leukocytes from normal individuals.[19] These include:

1 T-cells which no longer suppress if precultured without stimulus for 24 or 48 hours.[19]
2 Indomethacin-sensitive inhibition by 'adherent' cells, probably monocytes (mediated by prostaglandins).[19]
3 Indomethacin-insensitive inhibition by adherent cells.[19]
4 Suppression triggered by lipid-rich components, common to all mycobacteria and acting on cells from all normal individuals.[20,21]
5 Cells which, when precultured with antigen and then treated with mitomycin-C, will inhibit the response to the same or different antigens, of fresh cells from the same donor.[22]

Mechanisms 1[23], 2[24] and 4[21] are not increased in cell populations from any part of the leprosy spectrum, or in tuberculosis.

Mechanism 3 may be increased because 'suppressor monocytes' have been reported in both leprosy[25,26] and tuberculosis.[27] It is not clear what relationship these cells bear to the

partially activated monocytes demonstrable in the blood of tuberculosis patients,[28] or to the 'suppressor' macrophages in the spleens of C57Bl/6 mice.[13,15]

Mechanism 5 is demonstrable using PPD, SKSD, or Candida antigen, and peripheral blood mononuclear cells from normal donors. It has recently been shown that this assay becomes positive with *M. leprae* antigen, using cells from normal people after prolonged exposure to leprosy patients.[29] It will be interesting to know whether it works with cells from patients.

Clearly none of these findings supports the idea that inappropriate suppressor cell activity contributes to the pathogenesis of leprosy. However, several groups have looked for triggering of suppressor cells by leprosy bacilli, hoping to find an effect using cells from patients, not demonstrable using cells from normal donors, and their results are suggestive, although conflicting and controversial. One problem has been the ability of all mycobacteria to inhibit *in vitro* proliferative responses of cells from all donors[18,19] (mechanism 4 above). However, Mehra and colleagues have found that Dharmendra lepromin does not have this property. It is probable that the extensive extractions with chloroform and ether which are involved in its preparation, remove the lipid-rich components responsible for the non-specific effect,[20] and perhaps reveal determinants which are not normally exposed. It is reported that this antigen will suppress the mitogenic response to Concanavalin A of mononuclear cells from lepromatous and borderline leprosy, but not from tuberculoid cases, or normal donors.[26,30] In further experiments[30] involving, unfortunately, mixtures of cells from Non-HLA-matched donors, the suppressors were said to carry an antigen (TH_2) which defines a subset of T-cells which appears identical to that defined by T5 and T8 and therefore analogous to the Lyt $2,3^+$ cells of the mouse (Table 1).

However, other groups using mixtures of cells from HLA-matched siblings have been unable[25,31] to confirm this finding, and Nath and her colleagues have reported that lepromin triggered suppression by cells from tuberculoid, but not from lepromatous cases.[25] It may be important that these authors did not use Dharmendra lepromin. However, this is not the only system in which cells from lepromatous cases appear to have less rather than more regulatory activity. Susan Watson (personal communication) has found that the $T8^+$ T-cells from these patients are defective in their capacity to suppress the response to Pokeweed mitogen, when compared to normal donors. (It is possible that Nath and her colleagues are detecting $T4^+$ suppressor cells, analogous to the Lyt 1^+ suppressors in the murine Leishmania model,[5] and if so they could, by analogy, turn out to be important.)

These findings are not necessarily incompatible with those of Mehra and her colleagues. Nevertheless this author's work is open to two types of interpretation. The optimistic view is that she has demonstrated the existence of one or more 'suppressor determinants' specific to *M. leprae*, which trigger an unbalanced suppressor cell proliferation. These cells could then suppress the response to other components of any organism which contained the 'suppressor determinant'. Such a mechanism could explain the ability of lepromatous patients to give strong skin-test responses to soluble antigens prepared from other mycobacterial species, while failing to respond to *M. leprae*, although it is rich in common antigens. An experimental model of this type has been described in relation to the responses to lysozyme in mice.[32] If this is correct, then removal of TH^+_2 or $T8^+$ cells, could be therapeutically useful.

However, the fact that many leprosy patients will give negative skin-test responses to leprosy antigen, while responding strongly to antigen preparations from other cross-reactive species, has now been explained simply, without any need for 'suppressor determinants'. Leprosy patients simply do *not* respond to the common antigens either *in vitro* or *in vivo*.[33] Thus their ability to respond to other mycobacterial species is due to their response to the species-specific components rather than to a lack of suppression of responses to the shared ones.

It is also possible that the determinant(s) which trigger the suppression in the work of Mehra and her colleagues are not specific to *M. leprae* and are merely exposed by the treat-

ment with organic solvents which is involved in the preparation of Dharmendra lepromin. Controls with other organisms, similarly treated, do not appear to have been performed, but are an obvious prerequisite for the suppressor determinant hypothesis.

The pessimistic view is that the suppressor cells which Mehra *et al.*[30] have demonstrated, like those seen following deliberate intravenous overload of mice with BCG,[10] are the consequence rather than the cause of dissemination. Indeed, these may be examples of a more general phenomenon. Thus at a workshop which took place during the spring (1982) meeting of the British Society for Immunology (chaired by Professor J H L Playfair), it was agreed that suppressor cells, which can be activated by specific antigen to exert non-specific suppressor effects, are commonly found in late disseminated infections with protozoa (malaria, leishmania), worms and bacteria, but that removal of such cells, when it has been achieved, does not alter the course of the disease. Thus the majority view[34] was that cells such as those described in disseminated murine mycobacterioses, or in blood of BL/LL[26,30] patients are consequences, not causes, of progressive disease.

Another approach to the study of suppressor cells in the mycobacterioses is to count the absolute numbers or percentage of cells with the suppressor phenotype (e.g. TH^{+}_{2}, $T5^{+}$ or $T8^{+}$) in peripheral blood lymphocyte populations from diseased individuals. It has, for instance, been observed that during ENL episodes there is a decrease in the number of cells carrying the suppressor phenotype, relative to the number of helpers.[35] But what does this mean? Presumably the blood carries lymphocytes from one site to another. Thus a transient decrease in suppressor cells in the peripheral blood could be due to decreased production of suppressor cells, or to increased sequestration of suppressor cells in the tissues. These two explanations have precisely opposite implications in terms of the role of suppressor T-cells in ENL.

Another possibility is the analysis by immunohistological techniques of the lymphocyte subpopulations infiltrating mycobacterial lesions. Thus it has been shown that a PPD skin-test site in a normal individual contains lymphocytes of both major phenotypes ($T4^{+}$ and $T8^{+}$) in the same ratio as in the blood (L Poulter, unpublished observations).

In conclusion, there is no doubt that suppressor cells are one of the most exciting areas of contemporary immunology, and it is now clear that in mouse and man, suppressor cells can be triggered by mycobacterial antigens. In both species suppressor cells with non-specific suppressor effects accompany disseminated disease, but it will be extremely difficult to prove that they are important for its pathogenesis. All immune responses are regulated and the demonstration of regulatory mechanisms in the laboratory does not prove that they were behaving in an abnormal manner in the donor. At present most workers are studying cells with non-specific suppressor effects. That is to say, cells which, when activated by mycobacterial antigen, will suppress responses not only to that antigen, but also to other stimuli.

Moreover, some authors study suppression of lymphoproliferative responses (the significance of which in terms of effector function is unclear) while others study suppression of totally unrelated antibody or cytotoxic T-cell responses. It may be that relevant suppressor cells will be found only when we study specific suppression of the relevant effector systems. The recent work of Liew *et al.*[5] is a hopeful pointer in this direction.

It is also important to remember that the initial defect which leads to the susceptibility of a lepromatous leprosy patient may not be over-active suppression. We can equally well hypothesize that over-activity of an inappropriate effector system leads to a failure to destroy bacilli and that the increasing bacterial load secondarily activates a normal suppressor response.

References

[1] Gershon RK, Kondo K. Cell interactions in the induction of tolerance: the role of thymic lymphocytes. *Immunol*, 1970; **18**: 723–37.

[2] Golub ES. Suppressor T-cells and their possible role in the regulation of autoreactivity. *Cell*, 1981; **24**: 595–6.

[3] Liew FY. Regulation of delayed type hypersensitivity to pathogens and alloantigens. *Immunology Today*, 1982; **3**: 18–23.

[4] Reinherz EL, Schlossman SP. Regulation of the immune reponse-inducer and suppressor T-lymphocyte subsets in human beings. *New Eng J Med*, 1980; **303**: 370–3.

[5] Liew FY, Hale C, Howard JG. Immunologic regulation of experimental cutaneous leishmaniasis. V. Characteristics of effector and specific suppressor cells. *J Immunol*, 1982; **128**: 1917–22.

[6] Asherson GL, Zembala M. The role of the T-acceptor cell in suppressor systems: antigen specific T-suppressor factor acts via a T-acceptor cell; this releases a non-specific inhibitor of the transfer of contact sensitivity when exposed to antigen in the context of I-J. *Ann NY Acad Sci* (in press).

[7] Collins FM, Mackaness GB. The relationship of delayed hypersensitivity to acquired antituberculous immunity. I. Tuberculin sensitivity and resistance to infection in BCG-vaccinated mice. *Cell Immunol*, 1970; **1**: 253–65.

[8] Rook GAW. Immune responses to mycobacteria in mice and man. *Proc Roy Soc Med*, 1976; **69**: 442–4.

[9] Rook GAW. The immunological consequence of antigen overload in experimental mycobacterial infections of mice. *Clin exp Immunol*, 1975; **19**: 167–77.

[10] Watson SR, Collins FM. Development of suppressor T-cells in mice heavily infected with mycobacteria. *Immunol*, 1980; **39**: 367–73.

[11] Bullock WE, Carlson EM, Gershon RK. The evolution of immuno-suppressive cell populations in experimental mycobacterial infection. *J Immunol*, 1978; **120**: 1709–16.

[12] Collins FM, Congdon CC, Morrison NE. Growth of *Mycobacterium bovis* (BCG) in T-lymphocyte-depleted mice. *Infect Immun*, 1975; **11**: 57–64.

[13] Klimpel GR, Henney CS. BCG-induced suppressor cells. I. Demonstration of a macrophage-like suppressor cell that inhibits cytotoxic T-cell generation *in vitro*. *J Immunol*, 1978; **120**: 563-9.

[14] Orbach-Arbouys S Poupon M-F. Active suppression of *in vitro* reactivity of spleen cells after BCG treatment. *Immunol*, 1978; **34**: 431–7.

[15] Schrier DJ, Sternick JL, Allen EM, Moore VL. Genetic basis of BCG-induced suppression of delayed hypersensitivity. *Nature* (Lond), 1981; **289**: 405–7.

[16] Lefford ML, Patel PJ, Poulter LW, Mackaness GB. Induction of cell-mediated immunity to *Mycobacterium lepraemurium* in susceptible mice. *Infect Immun*, 1977; **18**: 654.

[17] Alexander J. Adoptive transfer of immunity and suppression by cells and serum in early *Mycobacterium lepraemurium* infections of mice. *Parasite Immunol*, 1979; **1**: 159–66.

[18] Moore VL, Modnloch VM, Pedersen GM, Schrier DJ, Allen EM. Strain variation in BCG-induced chronic pulmonary inflammation in mice: control by a cyclophosphamide-sensitive thymus-derived suppressor cell. *J Immunol*, 1981; **27**: 339–42.

[19] Rice L, Laughter AH, Twomey JJ. Three suppressor systems in human blood that modulate lymphoproliferation. *J Immunol*, 1979; **122**: 991–6.

[20] Wadee AH, Sher R, Rabson AR. Production of a suppressor factor by human adherent cells treated with mycobacteria. *J Immunol*, 1980; **125**: 1380–6.

[21] Bahr GM, Rook GAW, Stanford JL. Inhibition of the proliferative response of peripheral blood lymphocytes to mycobacterial or fungal antigens by co-stimulation with antigens from various mycobacterial species. *Immunol*, 1981; **44**: 593–8.

[22] Borkowsky W, Valentine FT. The proliferative response of human lymphocytes to antigen is suppressed preferentially by lymphocytes precultured with the same antigen. *J Immunol*, 1979; **122**: 1867–73.

[23] Bahr GM, Rook GAW, Stanford JL, Lydyard PM, Bryceson ADM. The effect of delayed addition of antigen and 'E' rosetting on the proliferative response to mycobacterial

antigens of peripheral blood lymphocytes from normal individuals or from patients with tuberculosis or leprosy. *Immunol*, 1981; **44**: 585–91.

[24] Bahr GM, Rook GAW, Stanford JL. Prostaglandin-dependent regulation of the *in vitro* proliferative response to mycobacterial antigens of peripheral blood lymphocytes from normal donors and from patients with tuberculosis or leprosy. *Clin exp Immunol*, 1981; **45**: 646–53.

[25] Nath I, Van Rood JJ, Mehra NK, Vaidya MC. Natural suppressor cells in human leprosy: The role of HLA-D-identical peripheral lymphocytes and macrophages in the *in vitro* modulation of lympho-proliferative responses. *Clin exp Immunol,* 1980; **42**: 203–10.

[26] Mehra V, Mason LH, Fields RP, Bloom BR. Lepromin-induced suppressor cells in patients with leprosy. *J Immunol*, 1979; **123**: 1813–17.

[27] Ellner JJ. Suppressor adherent cells in human tuberculosis. *J Immunol*, 1978; **121**: 1573–79.

[28] King GW, Bain G, LoBuglio AF. The effect of tuberculosis and neoplasia on human monocyte staphylocidal activity. *Cell Immunol*, 1975; **16**: 389–95.

[29] Stoner GL, Atlaw T, Touw J. Belehu A. Antigen-specific suppressor cells in subclinical leprosy. *Lancet*, 1981; **ii**: 1372-7.

[30] Mehra V, Mason LH, Rothman W, Reinherz E, Schlossman SF, Bloom BR. Delineation of a human T-cell subset responsible for Lepromin-induced suppression in leprosy patients. *J Immunol*, 1980; **125**: 1183–8.

[31] Stoner GL, Mshana RN, Touw J, Belehu A. Studies on the defect in cell-mediated immunity in lepromatous leprosy using HLA-D-identical siblings. Absence of circulating suppressor cells and evidence that the defect is in the T-lymphocyte rather than the monocyte population. *Scand J Immunol*, 1982; **15**: 33–48.

[32] Adorini L, Miller A, Sercarz E. The fine specificity of regulatory T-cells. *J Immunol*, 1979; **122**: 871–7.

[33] Rook GAW, Stanford JL. The heterogeneity of the immune response to mycobacteria and the relevance of the common antigens to their pathogenicity. *Ann Immunol* (Inst Pasteur), 1981; **132D**: 155–64.

[34] Playfair JHL. Parasite immunology (in press).

[35] Bach M-A, Chatenoud L, Wallach D, Phan Dinh Tuy F, Cottentot F. Studies on T-cell subsets and functions in leprosy. *Clin exp Immunol*, 1981; **44**: 491–500.

Lepr Rev (1982) **53**, 313

Obituary

Dr A B A KARAT

F.R.C.P. London, F.R.C.P. Edinburgh, B.Sc. Madras

Medical research and leprosy research in particular have suffered a serious loss in the untimely death on 14 March 1982 of Dr Karat, an outstanding Indian leprologist. A brilliant student at the Christian Medical College, Vellore, Dr Karat qualified at Madras in 1959, and after postgraduate study in Britain with Sakuntala, his doctor wife, he returned to India in 1963 with the M.R.C.P. of both London and Edinburgh, to be joined by Mrs Karat who had been awarded the F.R.C.S. Such a partnership was ideally suited to the problems of leprosy, and in 1963 they accepted the posts of Head of Medicine and Surgery respectively at the Schieffelin Leprosy Research and Training Centre, Karigiri, South India.

The following 8 years were made remarkable by the breadth of Dr Karat's research interests; his energy, his keen and penetrating insight, his clarity of thought and the skill which he brought to bear on a range of leprosy problems.

The intensive study of leprosy in Gudyatham Taluk yielded a series of scientific papers on epidemiological subjects, made especially precious by the contributions of Dr (Mrs) Karat on surgical aspects. At the base hospital he demonstrated conclusively that it is possible to maintain experimental mouse populations in Indian conditions, and numerous and valuable bacteriological, pathological, and therapeutic studies on new leprosy drugs were the result.

In 1971 Dr and Mrs Karat moved to Bangalore, where he became Honorary Professor of Medicine at the University, and continued his leprosy research. Later he became a consultant physician in the United Kingdom. In addition to his work on leprosy, he also undertook research on diabetes, hypertension and acute and chronic renal failure. He was a member of the WHO Expert Leprosy Panel.

Dr Karat's contributions in many scientific journals are a lasting record to the memory of a great scientist and leprologist, but his memory is also precious in the minds and hearts of his many friends and students, who will never forget his devotion to his patients, his unfailing kindness and generosity to his colleagues, his capacity to inspire others to care for sufferers from leprosy, and the courage and faith with which he faced his last illness. All who had the privilege of knowing him join to offer Mrs Karat and his family their heartfelt sympathy.

T F DAVEY

0305–7518/82/053313 + 01 $01.00

Lepr Rev (1982) **53**, 314–316

Domiciliary and Field Work: Reports, News and Notes

[Due to continuing pressure on space from the number of original articles which await publication, we combine, in this number of the journal, various items under the above headings. *Editor.*]

We gratefully acknowledge receipt of the following reports:

LEPRA Annual Report, 1981; Leprosy Control in Malaŵi; from Dr Gjalt, Medical Director, PO Box 148, Lilongwe, Malaŵi and Rev P Garland, National Manager, PO Box 496, Blantyre, Malaŵi.

2 Sasakawa Memorial Health Foundation, Japan; The 3rd International Workshop on Leprosy Control in Asia, Taipei, Taiwan, ROC, 17–22 November 1980. SMHF, Sabokaikan, 2-7-5 Hirakawa-cho, Chiyoda-ku, Tokyo 102, Japan.

3 Indian Council of Medical Research; Annual Report of the Director-General, 1980–81, New Delhi, India.

4 Nepal; 2nd National Workshop on Leprosy Control, Kathmandu, Nepal, 9–11 November 1981. The Ministry of Health, Nepal.

5 Leprosy Control in Ethiopia; National Leprosy Control Project; Annual Report for 1981. The Ministry of Health, Addis Ababa, Ethiopia.

6 WHO; Special Programme for Research and Training in Tropical Diseases; Annual Report; TDR/AR(5)/81.1–O.V. *Overview*, ditto ch 8; *Leprosy*.

7 Armauer Hansen Research Institute; AHRI; Annual Report for 1981. AHRI, PO Box 1005, Addis Ababa, Ethiopia.

8 Sierra Leone; National Leprosy Control Program in Sierra Leone; Report for Jan–Dec 1981. Ministry of Health and Voluntary Agencies. PO Box 873, Freetown, Sierra Leone.

XII International Leprosy Congress, New Delhi, India; postponement to 1984

For reasons beyond the control of the ILA and the Organizing Committee, the Congress has been postponed until 20–25 February 1984.

Mozambique: Anti-Leprosy Campaign, 1982: Amici dei Lebbrosi*

This association has recently made an agreement with the Government of Mozambique for a 5-year programme involving leprosy and primary health care programmes for the whole country.

The International Federation of Anti-Leprosy Associations (ILEP) has appointed Amici dei Lebbrosi as the ILEP Co-ordinator for work in Mozambique.

*Since 1979, Amici dei Lebbrosi has also been known as Amici di Raoul Follereau. Address: 4 Via Borselli, 40135 Bologna, Italy.

0305–7518/82/053314 + 03 $01.00

The 5-year programme will require financing in the region of US $100,000 per year. Based on recommendations made in a report by the WHO Consultant, Dr Alfredo Abreu, it aims to carry out extensive case-finding over the 55 districts, to register and treat the majority of leprosy cases, and to stress the use of rehabilitation to prevent and decrease the number of disabilities.

At the same time, this work will be part of a primary health care programme emphasizing health education with prevention, and integrated with the campaigns against the more dangerous endemic diseases.

The national anti-leprosy campaign will start early in 1982. It represents a major commitment for Amici dei Lebbrosi, as well as being an important contribution to the development of health services in Mozambique.

ILEP; Catalogue on Training (1982)

This valuable catalogue from ILEP in London provides information on courses at the major training centres during 1982; these are – ALERT, Bamako, Bauru, Carville, Dakar/Fann, Fontilles, Karigiri, Wau and Yaounde. Available from ILEP, 234 Blythe Road, London W14 0HJ, England.

WHO; Report of the Meeting on Social and Economic Aspects of Leprosy, Kuala Lumpur, 1–4 December 1981.

Main headings: objectives, review of issues, research topics, guidelines, strategies, strategic plan, conclusion and recommendations. TDR/SER-LEP/KL/81.3, WHO, Geneva, Switzerland.

TDR; Special Programme for Research and Training in Tropical Diseases; Newsletter

The April 1982 issue (No 17) reviews the testing of purified armadillo-derived *M. leprae* in man and progress in the THELEP field trials. The May 1982 issue (No 18) has a section on 'The Six Groups of Diseases – Five Years Later' and gives particular attention, under leprosy, to drug and vaccine trials. TDR, WHO, 1211, Geneva 27, Switzerland.

***Leprosy Scientific Memoranda* (LSM); resumption under Leonard Wood Memorial**

Due to the discontinuance of NIH funding, the last issue of LSM was in July 1981, but it has now been revived under the auspices of the Leonard Wood Memorial, with a partial grant from CIBA-GEIGY. The price of a subscription is as before – a minimum of one submission per year. Executive Director, Leonard Wood Memorial (American Leprosy Foundation), 11600 Nebel Street, Suite 210, Rockville, Maryland 20852, USA.

PATH; Program for Appropriate Technology in Health, Seattle, USA

Non-profit, non-governmental organization committed to the development, promotion and introduction of technology for primary health care programmes in developing countries. Established in 1979. Priorities include technologies or products associated with – diarrhoeal diseases, immunization, tropical diseases, nutrition, family planning, maternal and child care,

health and essential drugs. PATH, Canal Place, 130 Nickerson Street, Seattle, Washington 98109, USA.

AHRTAG; How to make hand grips

A poster which folds into a booklet and explains how hand grips can help disabled people to hold hand tools, brushes, etc. Free, but enclose stamped addressed label if you live in UK; AHRTAG, 85 Marylebone High Street, London W1M 3DE, England.

The Heiser Program for Research in Leprosy

The Director has issued details of the usual awards available under the following headings – Postdoctoral research fellowships; research grants and visiting research awards. Applications for 1983 should be made by 1 February 1983. A progress report is also available on the first five years of research sponsored by this Program. Apply to the Director, the Heiser Program for Research Leprosy, 450 East 63rd Street, New York, New York 10021, USA.

Correction: 'The Evaluation of Nerve Damage in Leprosy'

Sir, In the June 1982 issue of *Leprosy Review* this document was published as a 'special article' with myself named as the author.

This is misleading. The document represents the findings and suggestions of a workshop on neuritis held at Karigiri in 1980. As chairman of the workshop I had to take the major responsibility to produce the document in a form that was acceptable for publication; it was never my intention to pose as the originator or to present it as my personal ideas.

I would like to clarify that the title should read 'The Evaluation of Nerve Damage in Leprosy. Report of a workshop held at the Schieffelin Leprosy Research and Training Centre, Karigiri, 12 to 14 March 1980. Prepared for publication by J M H Pearson.'

Dhoolpet Leprosy Research Centre,
Hyderabad 6, India

J M H PEARSON

[We regret this misunderstanding and are grateful to Dr Pearson for drawing attention to an error which will be carefully adjusted in the Index of this volume. *Editor.*]

Errata

Please note the following corrections to the paper by E VAN PRAAG & S A MWANKEMWA. 'A prevalence survey on leprosy and the possible role of village 10-cell leaders in control in Muheza District, Tanzania.' *Lepr Rev*, 1982; **53**: 27–34.

page 27, address for E Van Praag is now Public Health Advisor, Ministry of Health, c/o POB 166, Dacca, Bangladesh.
page 31, table 1, column 1, *for* 0–1 *read* 0–5
line 1, *for* 1:10 *read* 1.9:1
page 32, table 5, column 1, *for* 25 *read* ⩽ 25

Lepr Rev (1982) **53**, 317–318

Letters to the Editor

LEPROSY, ONCHOCERCIASIS, DIETHYLCARBAMAZINE AND THE MAZZOTTI REACTION

Sir,

Whilst working in the Southern Sudan (1979–80) in an area endemic for both leprosy and onchocerciasis, we had the opportunity to examine a large number of patients with onchoceriasis and borderline leprosy, particularly borderline-lepromatous; BL on the Ridley–Jopling scale of whom we noted adverse reactions closely following the administration of diethylcarbamazine (DEC), both for the Mazzotti test and for treatment, as noted in a personal communication by Emilia Odé from the Cameroon in 1976.[1] These included skin and nerve lesions suggestive of reversal (upgrading) reaction, and they responded to appropriate treatment with steroids or other anti-reaction drugs. In view of the very large number of factors which may precipitate reactions in borderline patients, and the difficulty of ascertaining the full medical history, including drug intake, it is difficult to be sure that the drug was the sole cause in all instances, but the association was strongly suggestive in many of our cases.

A matter of additional interest in relation to these two diseases and the use of DEC is that in a few patients with lepromatous leprosy, we observed a suppression of the Mazzotti reaction, similar to that described by Meyers and Connor in 1975[2] and an absence of killing of microfilariae. A typical patient was a 45-year-old male, on regular dapsone treatment 100 mg per day for 2 years, with microfilarial counts as follows: eye 8/mg; scapula 153/mg; iliac crest 230/mg; calf 363/mg; upper arm 164/mg and lower arm 65/mg. A slight concurrent infection with *D. perstans* was also found in the blood. There was no rise of blood eosinophils and the urine and stool were negative for parasites. There was one onchocercoma palpable at the waist only. A Mazzotti test with 50 mg DEC produced absolutely no effect, but 3 hours later we recorded a microfilaruria, 10 out of 28 forms being alive in the sediment. Treatment was started with 50 mg DEC daily, increasing to 6 × 50 mg daily within a period of one week. From day 10, 8 × 50 mg was given daily up to day 24. Several examinations of blood revealed only an unchanged *D. perstans* infection and there was no eosinophilia either during or after treatment. Skin biopsies were taken 5 days and 17 days after the start of DEC treatment and we are grateful to the Armed Forces Institute of Pathology, Washington DC for the following reports.

5 day biopsy '. . . The most spectacular feature is the large number of microfilariae of *O. volvulus* in the upper dermis. None of these is degenerating or centred in a focus of inflammatory infiltrates. It is surprising none is degenerating after 5 days of DEC therapy. Nor do we see any evidence of any microfilariae migrating into the epidermis. These findings, however, are consistent with your clinical observation that there was no Mazzotti reaction and no microfilaricidal treatment response. Changes of leprosy are present with some inflammatory changes of nerves, occasional acid-fast bacilli in nerves and clumps of acid-fast bacilli in the walls of dermal vessels.'

17 day biopsy '. . . There are many microfilariae in the upper dermis. None is degenerated or surrounded by inflammatory cells. The remarkable feature is the absence of a reaction to the diethylcarbamazine. The number and distribution of microfilariae suggests that the DEC has had no effect.'

0305–7518/82/053317 + 02 $01.00

It must be recorded that this absence of response on Mazzotti testing and on treatment with DEC was not invariable in our lepromatous patients, but this case and a few others suggest that the subject may be worth further study. A similar observation has recently been made on a large series of patients in Bamako, Mali,[3] in which it was also observed that onchocerciasis was commoner in patients with leprosy than in the general population.

P STINGL and MARIA STINGL

8924 Steingaden
Lechbruckstrasse 10
Germany

References

1 McDougall AC. Onchocerciasis and streptocerciasis in patients with leprosy. *Trans Roy Soc Trop Med Hyg,* 1977; **71**: 360–1.

2 Meyers WM, Connor DH. Onchocerciasis and streptocerciasis in patients with leprosy. Altered Mazzotti reaction. *Trans Roy Soc Trop Med Hyg,* 1975, **69**: 524–525.

3 Penchenier L, Louvet M. Gridel F, Therizol-Ferly M. Etude paraclinique de l'onchocerose en population lépreuse et non lépreuse. *Bull Soc Path Ex*, 1981; **3**: 273–83.

LEPROSY AND PREGNANCY

Sir,

Duncan *et al.* have recently reported that onset, relapse or deterioration of clinical leprosy is especially liable to occur during pregnancy, in particular during the third trimester (*Lepr Rev*, 1981; **52**: 245–62). They suggest this could be associated with depression of cell-mediated immune responses during that period.

Whereas the accumulated evidence (*cf.* references in Duncan *et al.* paper) is consistent with pregnancy as an important risk factor in leprosy, it may be useful to point out a methodological problem which makes interpretation of the data very difficult. Women generally have more frequent contact with health services when they are pregnant or lactating, than at other times. Given this situation, even if there were no true association between leprosy and pregnancy, an apparent or observed association between them is to be expected. This is especially true in areas with high fertility, where women spend much of their lives either pregnant or lactating. A proper control group is required, consisting of non-pregnant and non-lactating women followed as closely as is the pregnant or lactating group. I am aware of no study which has included such a control group. Furthermore, the observation that clinical onset or deterioration is especially liable to occur during the third trimester could also be due to the fact that pregnant women are most liable to contact health services during the latter stages of pregnancy (eg. Table 1 in Duncan *et al., op. cit.*). The way to avoid this bias is by presenting risks in terms of incidence rates by person months under observation, rather than by trimester of observed onset.

This letter is not intended to be unduly critical of Duncan *et al.*'s valuable contribution, but to point out methodological issues which might be addressed by future investigators of this important subject.

P E M FINE

London School of Hygiene and Tropical Medicine
Ross Institute of Tropical Hygiene
Keppel Street
London WC1E 7HT

Lepr Rev (1982) **53**, 319–320

Book Reviews

Common Skin Diseases in Malawi and their Management, by V Gooskens. Department of Dermatology, Queen Elizabeth Hospital, Blantyre, Malawi, 1979. Production supported by the Netherlands Government.

This is a 67-page paperback booklet 'for use in health centres and hospitals by medical assistants, clinical officers and doctors'. The chapter headings include: anatomy; functions and examination of the skin; the very common skin diseases; other common and not so common skin diseases; drugs for local application; closing words and useful addresses. Pages 13 and 14 contain a chart on which it is possible to correlate dermatological lesions such as macules, papules, bullae, excoriations, etc. with a range of diseases ranging through the alphabet from acne to vitiligo. Colour plates of high quality illustrate dermatitis, photo-allergic contact dermatitis, infective dermatitis, acneiform contact dermatitis, scabies, impetigo, candida-paronychia, type 1 lepra reaction, pellagra, onchocerciasis, fixed drug eruption and Kaposi sarcoma. This is a well-constructed booklet with potential value in the diagnosis and management of skin diseases not only in Malawi, but in many other countries of Africa. [Current availability uncertain, but enquiries to Revd P Garland, LEPRA, PO Box 496, Blantyre, Malawi.]

The Social Dimension of Leprosy; training manual for health workers, by Alicia Kaufmann, Sister Senkenesh Gebre Mariam and Jane Neville. Published by the International Federation of Anti-Leprosy Associations, London, 1981.

Professor K F Schaller, President of the ILEP Medical Commission writes the Foreword to this excellent publication, the main headings of which are: the case method to solve social problems; social concepts to analyse cases; patients, staff and stages of illness; communication skills in leprosy control and clues for case studies. This is an extremely well-presented and up-to-date account of the subject which deserves wide circulation. From ILEP, 234 Blythe Road, London W14 0HJ.

WHO; Chemotherapy of leprosy for control programmes. Technical Report Series 675, 1982.

This report of a study group, published in the *Technical Report Series* by WHO in Geneva, will be considered in detail in editorials in this journal in 1983 and the purpose of this note is merely to draw attention to its availability now, and to emphasize the crucial importance of the combined regimens advised. Following a review of the problems of dapsone resistance and persistence, the main headings are: drugs for multi-drug regimens; recommended chemotherapeutic regimens, operational aspects and research needs. WHO, 1211 Geneva 27, Switzerland.

Studies on Leprosy. Research Publication; Voluntary Health Services Medical Centre, Madras India.

This is a 120-page paperback by Dr N Veeraraghavan of the Research Unit on Leprosy, VHS Medical Centre, Adyar,

0305–7518/82/053319 + 02 $01.00

Madras–600 113, India, published in March 1982. Although this work covers many aspects of leprosy, including microbiology, host cells, immunology, drug testing, the armadillo and a vaccine, it is essentially aimed at the presentation of the author's studies on the *in vitro* growth of *M. leprae* (and *M. tuberculosis*). Whilst admiring the enthusiasm and enormous amount of work which has clearly gone into this publication it seems regrettable that the forthright claims to culture of the leprosy bacillus have not been presented in the medical press for expert comment and examination.

The Unquiet Eye: a diagnostic guide, by A J Bron, Reader in Ophthalmology in the University of Oxford. Glaxo Laboratories Ltd.

This is a paperback of 97 pages published 'as a service to doctors' in May 1981. It has 83 colour plates, illustrating – mainly for the general practitioner – a wide range of conditions which can be recognized and diagnosed, and then either treated by him or referred for specialist advice. The main sections include: a guide to techniques; interpretation of symptoms and signs; dry eye; ocular trauma; subconjunctival haemorrhage; conjunctivitis; keratitis; anterior uveitis; angle closure glaucoma; epscleritis and scleritis; the red eye with proptosis; the red lid; summary of treatment; ocular screening by the general practitioner; anatomy; list of useful diagnostic equipment and glossary. Available from Glaxo Laboratories Ltd, Greenford, Middlesex UB6 0HE, England.

Modern Genetic Concepts and Techniques in the Study of Parasites, Proceedings of the Symposium held in Geneva, 27–29 May 1980. 1981. 448 pages, 84 illustr, Hardbound Fr. 56.-- / DM 67.--. Published by Schwabe + Co, AG, Basel. *Note:* copies are available free of charge to institutions and scientists *in the developing endemic countries* on request from the Office of the Director of the Special Programme, 1211 Geneva, 27, Switzerland.

The meeting focused on basic molecular biology and genetics including the genetics of coexistence of parasites and man, genetic control of host response, susceptibility, resistance to infection, and genetic bases of variability in host response to infection. Hybridoma technology for production of monoclonal antibodies to parasite antigens, nucleic acid hybridization techniques for production of DNA probes and the use of recombinant DNA technology for production of large amounts of relevant antigens for diagnostic purposes and development of candidate vaccines were discussed. (Chapter 20, page 387 onwards is entirely devoted to *Genetic Aspects of Leprosy* by Morten Harboe, University of Oslo.)

AC MCDOUGALL

®Lamprene Geigy

Antileprosy drug with anti-inflammatory[1] properties

effective in the prevention[2] and treatment[3] of lepra (ENL) reactions

indicated as a part of combined therapy for the prevention and treatment of dapsone resistance in lepromatous and borderline leprosy[4].

1. Browne, S.G.: Lepr. Rev. 37, 141 (1966)
2. Azulay et al.: Lepr. Rev. 46 (Suppl.) 99 (1975)
3. Schulz, E.J.: Lepr. Rev. 42, 178 (1972)
4. Yawalkar, S.J., & Vischer, W.A.: Lepr. Rev. 50, 135 (1979)

011 LAM 7479 e

Leprosy Review Index

VOLUME 53 – 1982

CONTENTS

Printed in Great Britain at the Alden Press
Oxford, London and Northampton