Editorial

MACROPHAGE STIMULATION AND ACTIVITY IN LEPROMATOUS LEPROSY

The concept of activity, chronicity and regression in the lesions of lepromatous leprosy is relatively unexplored territory. By comparison with most infections, of course, leprosy is always chronic. However, it is generally accepted that in untreated lepromatous infections there is a wide range of variation in the morphological index, which is sometimes unaccountably low. Thus in a large multicentre drug trial based on 17 institutions which represented most of the main endemic areas of the world,[1] 44 out of 138 patients selected for having good active lesions were rejected, mainly on the grounds that their MI was less than 5, or their granulomas occupied less than 15% of the biopsy specimens. At one centre 7 out of 8 biopsies showed lesions with a granuloma of no more than 5%. On the other hand it is commonly found that in relapse, except in the very early stages, the lesions are uncommonly active.[2,3] However, while the level of activity in untreated leprosy is fairly uniform, in relapse it may vary greatly from lesion to lesion. As regards histoid lesions Wade[4] commented that the bacterial load in the particularly 'active' phagocytes was 'simply incredible'. Most subsequent writers have made the same observation, which raises the question of the relationship between the activity of leprosy bacilli and the activity of their host macrophages. In all of this we are considering LL lepromas in which there is no evidence of any difference within the immune spectrum to account for differences in the behaviour of the lesions.

High cell turnover granulomas

In lepromatous leprosy the macrophages are clearly not activated in any specific sense in the way they would be under the stimulus of an agent against which the host was immune, which is thought to be due to the mediation of T lymphocytes. However, there is an alternative sort of stimulation which is associated with high cell turnover as opposed to low turnover granulomas.[5] The turnover rate is due simply to the speed of entry of macrophages from the circulation and their division within the lesion, balanced in part by their

emigration from the lesion. The control of this rate of turnover is not fully understood, but an important factor is the nature of the inducing agent. Thus Freund's adjuvant or paraffin oil induces macrophages with a high cell turnover, measured by the rate of fall in the proportion of labelled macrophages in the lesion, whereas the relatively inert polymer carrageenan induces macrophages with a low cell turnover.[5] High turnover appears to persist as long as the irritation of the inducing agent persists,[6] after which the macrophage life span increase and the turnover rate declines. Such non-specific stimulation is associated with increased phagocytic potential,[7] though the increase is short-lived.[8]

Cytology of activity and regression

There is no way of measuring cell turnover directly in a human granuloma, but proliferative activity, as in histoid lesions,[9] has a similar significance. There is also the cytological approach. The stages in the evolution of mononuclear cells to macrophages and epithelioid cells under the stimulus of BCG have been described morphologically by Adams,[10] both by light and electron microscopy. This study was in guinea-pigs, but the appearances that correlate with degrees of stimulation are essentially similar in human cells of the mononuclear phagocyte series, with slight modifications. The evolution of nucleus and nucleolus is not quite so conspicuous in man, and in leprosy the form of the cytoplasm is greatly modified by the bulk of the bacilli and later, the accumulation of fatty debris (as in an oil granuloma). Viewing the course of a lepromatous infection in this context, at the earliest stage when bacilli are still few and mainly granular one sees granuloma cells some of which are not far removed from mononuclears with round, rather dark nuclei. Others show already some sign of stimulation, the nuclei being paler and the nucleolus more prominent. The cytoplasm is sparse and fairly solid because it has never held any large number of bacilli. The lesion may remain quiescent at this stage for a considerable period, or it may quite rapidly become fully active. The nuclei then are all in the stimulated state just described, though slightly larger than before, and the cytoplasm is bulkier with more bacilli and a little more foamy change, especially in LLp lesions. Regression comes about usually due to chemotherapy, but it may occur also in untreated patients with very long-standing disease (burn-out lepromas). There is much vesiculation of the very bulky cytoplasm due to the increase of fat which is partly of bacterial origin though some is due to cellular degeneration.[11, 12] All surface receptor sites are lost.[13] The surviving nuclei still show signs of moderate stimulation in some cases, but gradually they become pyknotic and disappear, leaving areas of non-nucleated foamy cytoplasmic debris. These changes are illustrated elsewhere.[14]

In BB leprosy the granuloma cells, by light microscopy, have the appearance

of 'immature' epithelioid cells,[10] though by electron microscopy they have the features of activated macrophages.[15] Further up the spectrum one encounters better developed epithelioid cells. But the best example of simple macrophage stimulation in leprosy is the histoid lesion.[3, 14] The nuclei are large and somewhat elongated (whether or not the cytoplasm is elongated). Though loaded with bacilli the cytoplasm is relatively solid because of the high cell turnover. Cellular proliferation accounts also, no doubt, for the expansile type of spread. Ultra-structural evidence of activity has also been obtained.[9, 16] Yet although the histoid lesion appears to be the extreme example of macrophage stimulation in leprosy, it is not a unique or invariable entity. Lesions with histoid features may be found in many cases that are not completely histoid.[2, 3, 17, 18] No evidence has been produced to support the view that they are due to mutant bacilli.[19]

Regulation of activity

It can be concluded, therefore, that some leprosy lesions exhibit cytological and proliferative evidence of a form of non-specific stimulation that is commonly associated either with adjuvants or with organisms which excite a strong immunological response. What is it that stimulates such a response in some cases of lepromatous leprosy, though without any apparent immunological enhancement? The question deserves to be formulated though it is difficult to answer.

The duration of the cellular response is related to the load on the macrophages.[6] It seems clear also that bacterial multiplication stimulates an influx of macrophages, which in lepromatous leprosy are probably the ideal host cells for bacterial multiplication. Thus one can envisage a self-perpetuating cycle in which bacterial multiplication stimulated an influx of more host cells which would favour a further increase of multiplication. But this would not explain why the hyperactive response is more common in relapse than in primary infections, or why the latter are often so chronic. Furthermore, one often gains a strong impression, though it has never been documented, that in relapse, at least, cellular activity is sometimes at variance with bacterial activity. There must be some other factor or factors in operation.

Immune complexes and antibody

Some of these points could possibly be explained by the involvement of immune complexes or antibody.[20] Immune complexes at antigen–antibody equivalence can induce granuloma formation, and an antibody excess enhances the process possibly due to its effect in delaying the degradation of the

complexes by the macrophages.[21] Thus high antibody levels might in theory help to explain both the cellular and bacteriological activity, and in part the immunological failure of lepromatous leprosy.[22] It would not be surprising if in relapse, which represents in effect a second infection, there might be a sharp rise in antibody levels, which on this hypothesis would stimulate bacteriological activity in those lesions where renewed activity was originating. But although there are a number of reports of raised antibody levels in lepromatous infections, especially before treatment and during reactions, the only study to deal with relapse was one on BT leprosy.[23] Nor, apparently, has there been any correlation of antibody levels, which vary widely, with degrees of activity in untreated patients. At present, therefore, there is no direct evidence to substantiate a governing role for bacterial antibody on the kinetics of the granuloma. However, Preston[24] found that mice susceptible to *M. lepraemurium* possessed a serum factor which suppressed the bactericidal performance of the macrophages. The hypothesis is plausible.

A self-perpetuating cycle

The role of antigenic load on macrophage performance is not likely to be less important than that of antibody, and it is a factor which is readily investigated. Clinico-pathological observations give strong grounds for thinking that the total antigenic load is directly correlated with immuno-depression, and that it must be one of the most important determinants of macrophage performance. Recent work provides immunological[25] and experimental[26] evidence that it is an important secondary cause for deficient T cell function. More antigen would of course produce more antibody.

The mechanics of macrophage control by lymphokines are outside the scope of this review, but there is one other immunological mechanism that cannot be overlooked. Schorlemmer *et al* (27) find that a common factor among agents that stimulate macrophages is an ability to activate complement by the alternative pathway. The enzymes which are released from the stimulated macrophages themselves cleave C_3, which is itself synthesized by the macrophages. A similar cycle involves factor B and cathepsin. Hence the agents which recruit macrophages are produced by the macrophages themselves, independently of serum factors.

Thus there appear to be multiple factors tending to produce a self-perpetuating cycle of enhancing activity, which is precipitated most frequently by the stimulus of relapse. If such a high level cycle of antigen–antibody–macrophage influx is the explanation for hyperactivity in lepromatous leprosy, then the slow development and low morphological index of some primary infections might be due, presumably, to the low level of the components which would be needed to start the cycle. The cases under consideration are those in

which the bacilli are already established at their site of optimal multiplication in the sub-papillary plexus of the dermis.[28] Thus neural protection, which is thought to favour bacilli in the early dormant phase of lepromatous infections (as well as in tuberculoid leprosy), would not be relevant to the situation in question. But it might mean that bacilli which had thrived up to a certain point in a protected environment lacked the capacity for rapid advance outside the environment.

From the foregoing discussion it would appear that the prime factors that stimulate or allow activity in lepromatous leprosy, cellular and bacterial, are vagaries of certain factors that are amongst those responsible for inducing immuno-depression. For this reason alone the question of activity deserves further study. More would be learnt about it if it were customary to record the approximate level of bacteriological and histological activity of immunological studies on leprosy patients.

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Lepr Rev (1980) **51**, 117–123

HLA–DR antigens in tuberculoid and lepromatous leprosy

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Received for publication 19 November 1979

Summary The frequencies of distribution of six histocompatibility antigens of the HLA–DR locus were determined in 38 Mexican patients with lepromatous leprosy and in 19 Mexican patients with tuberculoid leprosy. These were compared with antigen frequencies of 174 Mexicans who did not have leprosy. No evidence of an association between HLA–DR antigens and leprosy could be found. In tuberculoid subjects HLA–DRW2 was more common than in controls, 32% and 15% respectively. Although this difference was not statistically significant, it was in accord with another report of a significant increase in HLA–DRW2 among patients with tuberculoid leprosy. Furthermore, frequencies for 16 HLA–A, 23 HLA–B and five HLA–C antigens did not differ significantly in the two groups of patients as compared with controls.

Introduction

An association has been sought repeatedly between leprosy and antigens of the HLA–A and HLA–B loci of the major histocompatibility complex (Chan *et al.*, 1979;[1] Dasgupta *et al.*, 1975;[2] de Vries *et al.*, 1976;[3] Escobar-Gutierrez *et al.*, 1973;[4] Greiner *et al.*, 1978;[5] Kriesler *et al.*, 1974;[6] Massoud *et al.*, 1978;[7] Rea *et al.*, 1976;[8] Reis *et al.*, 1974;[9] Smith *et al.*, 1975;[10] Takata *et al.*, 1978;[11] Thorsby *et al.*, 1973;[12] and Youngchaiyud *et al.*, 1977[13]). The at least 13 studies reported to date collectively attest to the attractiveness of evidence suggesting that susceptibility to, and mode of expression of, leprosy is under genetic control (Chakravartti and Vogel, 1973;[14] Newell, 1966;[15] and Spickett 1962a,[16]

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0305–7518/80/020117 + 07 $01.00/0

1962b[17]). In four of these 13 studies statistically significant associations with an HLA–A (Kriesler *et al.*, 1974[6]) or HLA–B (Chan *et al.*, 1979;[1] Takata *et al.*, 1978;[11] and Thorsby *et al.*, 1973[12]) antigen were found, after correction by multiplying the p-value by the number of specificities tested. Greiner *et al.* (1978)[5] reasoned that this multiplying method of correction was not adequate because frequencies of various antigens are not independent; instead, relative risk was calculated as a measure of the significance of an association. However, whatever method was used to establish statistical significance, even among studies reporting significance, there has been no consistent association of a particular HLA–A and HLA–B antigen with any particular type of leprosy or with leprosy in general. Differing pressures for linkage disequilibrium in differing populations was an attractive explanation for the discordant, but yet significant findings (de Vries *et al.*, 1976).[3]

Study of HLA–A and HLA–B haplotype inheritance has provided further evidence that susceptibility to, and type of, leprosy may be influenced by genes within the major histocompatibility complex (de Vries *et al.*, 1976;[3] Fine *et al.*, 1979[18]).

Because the HLA–D and HLA–DR loci are nearer to the hypothetical immune response (Ir) gene than are HLA–A, –B, or –C loci, and because antigens of HLA–D or HLA–DR loci may show a closer association to a particular disease than can be detected by typing for HLA–A, –B, or –C antigens (Rachelefsky *et al.*, 1976;[19] and Reinertsen *et al.*, 1978[20]), it is logical that an association of HLA–D and HLA–DR antigens with leprosy has been sought. Stoner *et al.* (1978)[21] tested *in vitro* lymphoproliferative responses to *Mycobacterium leprae* in HLA–D identical and non-identical siblings of patients with lepromatous leprosy; finding that the HLA–D identical siblings responded as well as the HLA–D non-identical, they concluded that the *M. leprae* unresponsiveness of lepromatous patients was not the result of an HLA–D or –D-linked gene. In a preliminary report, de Vries *et al.* (1979)[22] found no evidence of an association between lepromatous leprosy and HLA–DR antigens; however, a statistically significant increase in HLA–DRW2 frequency in tuberculoid patients was present. We herein report our study of HAL–DR antigen frequencies in Mexican patients with leprosy.

Patients and methods

Patients were classified according to the histological and clinical criteria of Ridley and co-workers (Ridley, 1974; Ridley and Jopling, 1962; and Waters, 1969[25]). Because of the high incidence of erythema *nodosum leprosum* and Lucio's reaction, a histological distinction between polar and subpolar lepromatous leprosy could not be made (Ridley, 1974;[23] Ridley and Waters, 1969[25]). However, by clinical criteria all patients classed as lepromatous

were polar lepromatous (Ridley and Waters, 1969).[25] Thus 36 of 38 patients had or had had either erythema *nodosum leprosum* of Lucio's reaction, but never a reversal reaction. Also no patient had had a well-defined plaque clinically characteristic of subpolar lepromatous leprosy (Ridley and Waters, 1969).[25] Three of the 38 lepromatous patients showed a slight unilateral contraction of the fourth and fifth fingers but without associated asymmetrical sensory loss or muscle atrophy; other than this there was no suggestion of nerve trunk palsies. Finally, 18 of the 38 lepromatous subjects were known to have had diffuse, non-nodular lepromatous leprosy prior to beginning chemotherapy.

All of the tuberculoid patients were classified as BT (borderline with tuberculoid features). Most were typical of the BT classification. One patient showed some TT (polar tuberculoid) features by histological criteria and others TT by clinical criteria; but none were TT by both clinical and histological criteria.

All patients were Mexican-born or of bilateral Mexican-American ancestry. Controls were Mexican and Mexican-American blood bank and tissue transplant donors.

The microlymphocytotoxic method was employed (Mittal *et al.*, 1968).[26] B-lymphocytes were separated from T-lymphocytes by adherence to nylon wool. Six HLA–DRW antigens were sought, 1–5 and 7 (HLA–DRW6 was sought but is not reported because it probably does not exist). In addition to HLA–DR, 16 HLA–A, 23 HLA–B and five HLA–C antigens were sought.

Statistical analysis employed the ψ^2 test with the Yates' correction.

Results

The results are summarized in Table 1 for HLA–DR and in Table 2 for HLA–A, –B and –C antigens.

HLA–DRW2 was more common in tuberculoid patients (32%) than in controls (15%), but the difference was not statistically significant even uncorrected, $\psi^2 = 2.33$, $p > 0.1$. In the 38 lepromatous patients there was not even a suggestion of a genuine difference in antigen frequency distribution as

Table 1. Frequencies (%) of distributions of HLA–DR antigens in patients and controls

Antigen	Controls (174)	Tuberculoid Leprosy (19)	Lepromatous Leprosy (38)
HLA DRW 1	20	11	21
2	15	32	13
3	20	26	13
4	38	26	42
5	15	16	13
7	14	16	16

Table 2. Frequencies (%) of distribution of HLA–A, –B and –C antigens in patients and controls

Antigen	Controls (332)	Tuberculoid Leprosy (19)	Lepromatous Leprosy (44)
HLA–A1	12	11	7
A2	50	32	64
A3	9	21	14
A11	14	16	2
A25	2	0	0
A26	8	21	7
A28	19	26	23
A29	9	0	11
AW23	5	5	2
AW24	28	32	32
AW30	7	5	11
AW31	10	11	14
AW32	7	5	2
AW33	5	5	2
AW34	0	0	0
AW36	0	0	0
HLA–B7	8	11	9
B8	6	5	11
B13	1	0	5
B14	11	16	14
B15	9	0	7
B17	5	0	5
B18	6	16	2
HLA–B27	6	0	0
B37	2	5	2
B40	21	16	18
BW22	0	0	0
BW35	33	37	36
BW38	11	21	14
BW39	10	5	2
BW42	2	11	0
BW44	16	11	11
BW45	2	0	7
BW49	4	0	2
BW50	4	0	5
BW51	12	5	11
BW52	8	0	2
BW53	0	0	0
BW54	1	0	2
HLA–CW1	8	5	0
CW2	8	11	0
CW3	25	26	16
CW4	31	47	30
CW5	0	0	0

compared with controls; the greatest difference was with HLA–DRW3 and had a p-value of greater than 0.3. Likewise, antigen frequencies for the HLA–A, –B and –C loci did not differ significantly in the two groups of patients and in the controls.

Discussion

No evidence of an association between an HLA–DR antigen and leprosy could be found. However, the finding of a higher incidence of HLA–DRW2 in tuberculoid patients than in controls was in accord with the results of de Vries *et al.* (1979).[22] Although not statistically significant with these small numbers, our data is consistent with an association between HLA–DRW2 and tuberculoid leprosy. Furthermore, the similarity of antigen frequencies in the lepromatous patients and in the controls indicates that stratification between the leprosy patients and the controls was unlikely. Differences between our findings and those of de Vries *et al.* (1979)[22] could be explained by differences in patient classification or pressures for linkage disequilibrium. Also genetic differences might be anticipated, as part of an explanation for the high prevalence rate of tuberculoid leprosy among populations studied by de Vries *et al.* (1976,[3] 1979[22]), 10 per 1000 or more, but the low prevalence rate of tuberculoid leprosy among Mexicans (Villarreal, 1979)[27] 0.03 per 1000 – a difference of over two orders of magnitude.

Two studies of HLA–DR antigen frequencies (de Vries *et al.*, 1979,[22] and the present study) and the study by Stoner *et al.* (1978)[21] have provided no evidence of an association between lepromatous leprosy and antigens of the HLA–DR and HLA–D loci. These negative findings do not undo the evidence that susceptibility to lepromatous leprosy is under genetic control, but suggest that the critical gene(s) will not be found in the major histocompatibility complex. That is to say, the controlling gene(s) for lepromatous leprosy will prove to be neither an HLA antigen nor linked to an HLA antigen. Perhaps leprosy in man may be analogous to *Listeria monocytogenes* infection in mice (Skamene *et al.*, 1979),[28] where resistance and susceptibility are under genetic control outside of the H-2 complex, but footpad reactions to *L. monocytogenes* antigens appear to be linked to the H-2 complex.

Acknowledgements

This study was supported in part by a research grant from The Victor Heiser Awards for Research in Leprosy. Access to the patients of the US Public Health Service Clinic in San Pedro, California and the San Diego County Public Health Clinic was graciously provided by Dr John Gebhard and Dr Antonio Lopez.

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Lepr Rev (1980) **51**, 125–135

Demonstration of antibodies against *Mycobacterium leprae* both in immunoglobulin G and M in sera from pregnant and non-pregnant lepromatous leprosy patients

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Received for publication 1 November 1979

Summary Antibodies against *M. leprae* antigen 7 have been shown to consist of both immunoglobulin G and M in a lepromatous leprosy serum pool and in individual sera from patients with active lepromatous leprosy. Various implications of the occurrence of anti-*M. leprae* antibodies in several immunoglobulin classes are discussed, particularly their use as an indicator of transfer of *M. leprae* antigens or of live leprosy bacilli to the foetus during pregnancy. With the present techniques, no IgM antibodies against *M. leprae* antigen 7 could be detected in several cord sera from babies born of mothers with active lepromatous leprosy.

Introduction

About 20 distinct antigenic components have so far been detected in *Mycobacterium leprae* by crossed immunoelectrophoresis (CIE) using rabbit antisera against purified armadillo-grown leprosy bacilli (Harbo *et al.*, 1977a;[1] 1977b;[2] Closs *et al.*, 1978).[3] One of these components, *M. leprae* antigen 7, has been purified and labelled with ^{125}I, and this preparation has been used to develop a radio-immuno-assay (RIA) for detection and quantitation of anti-*M. leprae* 7 antibodies (Melsom *et al.*, 1978;[4] Yoder *et al.*, 1979).[5]

Patients with lepromatous leprosy have on average the highest concentration of antibodies towards *M. leprae* antigen 7 in their sera with a steady decline towards the tuberculoid end of the spectrum. Within each group there

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0305–7518/80/020125 + 11 $01.00

is a large variation in concentration of anti-*M. leprae* antigen 7 in sera from individual patients (Yoder *et al.*, 1979).[5]

In lepromatous leprosy patients there is only a small decline in anti-*M. leprae* antigen 7 activity during one and a half years of treatment with DDS (Melsom *et al.*, 1978),[3] while in tuberculoid leprosy the decline appears to occur faster (Yoder *et al.*, 1979).[5]

The specificity of anti-mycobacterial antibodies in leprosy has been characterized by various gel precipitation techniques, particularly CIE with patient serum in the intermediate gel. The number of antibody specificities is lower in tuberculoid than lepromatous leprosy. However, even in most cases of lepromatous leprosy the antibodies are directed against only a limited number of antigenic components of bacillus (Axelsen *et al.*, 1974;[6] Myrvang *et al.*, 1974;[7] Kronvall *et al.*, 1975).[8]

Patients with active lepromatous leprosy have an increased concentration of IgG and possibly also of IgM and IgA in their sera (Gupta *et al.* 1978).[9] Antibodies towards *M. leprae* has been demonstrated but not quantitated in both IgG and IgM class (Abe *et al.*, 1972)[10] but antibodies of IgA class have not yet been demonstrated.

The present RIA is based upon using protein A on the surface of Cowan I strain of staphylococci (NCTC 85308) as solid phase to separate free antigen from antibody-bound antigen. It was previously believed that protein A could only bind IgG immunoglobulins of subclass IgG1, IgG2 and IgG4 (Kronvall and Williams, 1969).[11] It has later been shown that protein A also can bind IgA of subclass IgA2 and IgM of subclass IgM2 (Harboe and Følling, 1974;[12] Saltvedt and Harboe, 1976).[13] The assay is therefore now also expected to detect IgA2 and IgM2 antibodies.

The purpose of the present work was to use this sensitive RIA to establish if antibodies against *M. leprae* antigen 7 occurred both in IgG and IgM in leprosy.

Materials and methods

PATIENT SERA

A serum pool was made from 40 sera obtained from patients suffering from lepromatous leprosy (LL, LI and BL) who had been either newly diagnosed or had been treated with DDS for less than 6 months. Sera were also collected from 4 mothers suffering from active lepromatous leprosy (LL, LI and BL) (Ridley and Jopling, 1966;[14] Ridley and Waters, 1969;[15] Myrvang *et al.*, 1973)[16] and their babies, from one mother suffering from tuberculoid leprosy and her baby, and from one healthy mother and her baby. The samples were taken at delivery from the mother and from the cord of the newborn baby.

PREPARATION AND LABELLING OF *M. LEPRAE* ANTIGEN 7

M. leprae purified from infected armadillo liver by Draper's technique (Draper, 1976)[17] were provided by R.J.W. Rees and P. Draper through the IMMLEP programme. ^{125}I-labelled *M. leprae* antigen 7 was made by electrolytic iodination and tested for purity by crossed immunoelectrophoresis and autoradiography. The properties of the presently used preparation corresponded closely to those of the preparation described in detail previously (Melsom *et al.*, 1978).[4]

RADIO-IMMUNO ASSAY (RIA)

The procedure described previously for assay of antibodies against *M. leprae* antigen 7 was used. In brief, the fractions after density gradient ultracentrifugation were diluted 1:50 in phosphate buffered saline (PBS) containing 0.2% bovine serum albumin (BSA). 100 µl of these dilutions were added to 100 µl of labelled *M. leprae* antigen 7, and protein A containing staphylococci were used as solid phase to separate labelled antigen 7 bound to antibody from free labelled antigen 7 (Melsom *et al.*, 1978).[4]

DENSITY GRADIENT ULTRACENTRIFUGATION

The IgM fraction was separated from IgG in human serum by zonal ultracentrifugation on a 10–40% sucrose density gradient in Tris-NaCl buffer of pH 8.0. When the effect of the acid pH was tested, a similar sucrose gradient in 0.1 M/glycine-HCl buffer of pH 3.0 was used (Hannestad, 1967).[18] Ultracentrifugation was carried out in a Spinco L-50 preparative ultracentrifuge equipped with a SW 65 K rotor 18 hours at 4°C at 36,000 rev./min. Fractions of 4–5 drops each were collected from a pinhole in the bottom of each tube.

DETERMINATION OF IGM AND IGG CONCENTRATIONS

The IgM and IgG concentrations were determined in the fractions after density gradient ultracentrifugation by single radial diffusion method as previously described (Melsom *et al.*, 1979).[19]

REDUCTION WITH 2-MERCAPTOETHANOL

To abolish antibody activity in the IgM fraction, reduction with 2-mercaptoethanol was performed as follows: To 100 µl of serum, 100 µl of 0.9% NaCl and 7.5 µl of 2-mercaptoethanol were added. The mixture was incubated at 20°C for 2 minutes and layered over a sucrose gradient followed by immediate start of the centrifuge. This provided a concentration of 0.5 M.

2-mercaptoethanol in the sample for reduction and did not lead to solidification of serum which occurred when higher concentrations of 2-mercaptoethanol or undiluted serum were used (Solheim and Harboe 1972).[20]

Results

When the lepromatous leprosy serum pool was subjected to density gradient ultra-centrifugation and the fractions tested by RIA, antibody activity against *M. leprae* antigen 7 was found in two distinct peaks; denoted peak 1 and peak 2 in Fig. 1. The concentration of IgM and IgG as determined by single radial diffusion in the different fractions, is also indicated in the figure. IgM was clearly separated from IgG. As seen in Fig. 1, maximal IgM concentration corresponded to maximal antibody activity in peak 1 and the distribution of IgG concentration corresponded to antibody activity in peak 2.

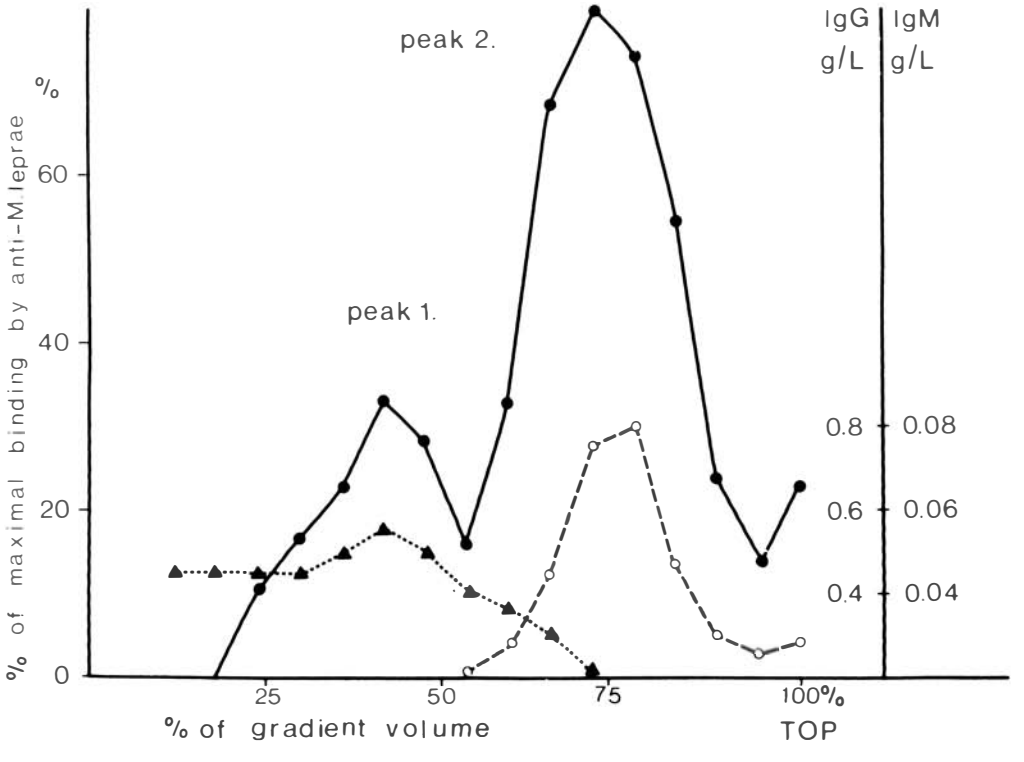

Figure 1. ●—● antibody activity against *M. leprae* antigen 7, ▲---▲ IgM concentration and ○---○ IgG concentration in different fractions after density gradient ultracentrifugation of LL serum pool.

The lepromatous leprosy serum pool was then tested in the same way after reduction of the serum with 2-mercaptoethanol. RIA with labelled *M. leprae* antigen 7 showed virtually no antibody activity corresponding to peak 1 after reduction of the serum with 2-mercaptoethanol. Nor could IgM be detected in the rapidly sedimenting fractions, while both peak 2 antibody activity and the IgG peak were found in the usual location (Fig. 2). The same results are seen in Fig. 3 where one individual serum has been treated with 2-mercaptoethanol. No antibody activity against *M. leprae* antigen 7 nor any IgM could be detected in the rapidly sedimenting fractions.

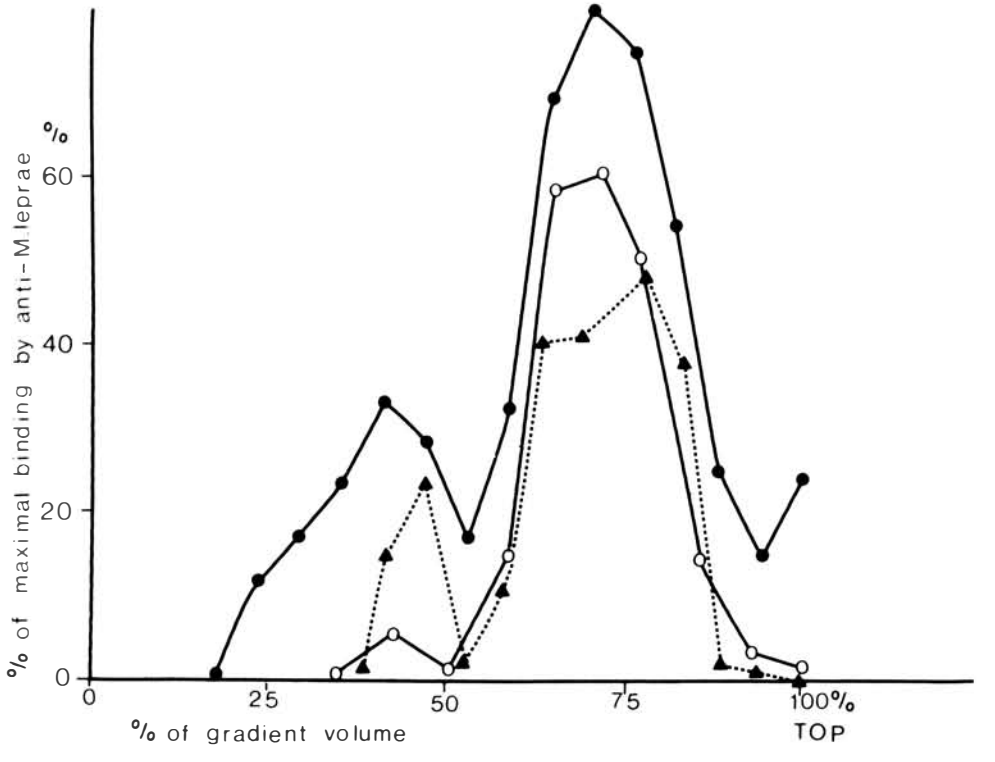

Figure 2. Antibody activity against *M. leprae* antigen 7 in fractions after density gradient ultracentrifugation of ●—● LL serum pool at pH 8.0, ○—○ LL serum pool at pH 3.0 and ▲---▲ LL serum pool after reduction with 2-mercaptoethanol.

Pretreatment with low pH would dissolve immune complexes consisting of labelled *M. leprae* antigen 7 and corresponding antibodies and other types of IgG complexes. At pH 8.0 such complexes would sediment faster than the bulk of monomeric IgG and together with other faster sedimenting components such as IgM. To exclude that the antibody activity in peak 1 consisted of IgG complexes, one individual serum from a mother suffering from lepromatous leprosy

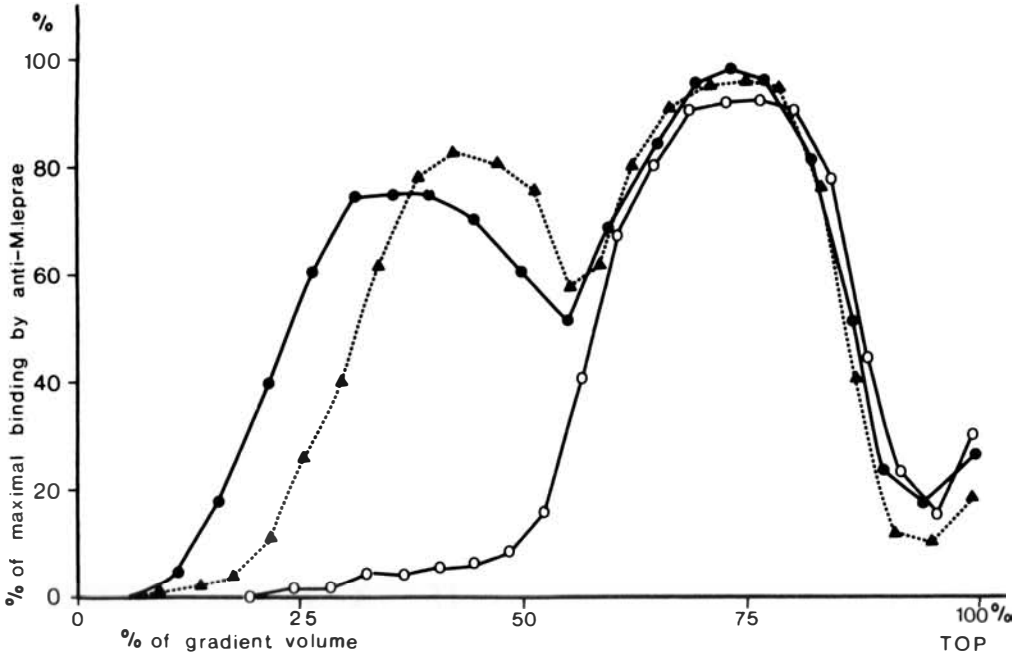

Fig 3. As for Figure 2 but with serum 242/76 from a patient with active lepromatous leprosy.

was fractionated by density gradient ultracentrifugation at pH 3.0. IgM and IgG were still demonstrated in fast and slow sedimenting fractions respectively. The *M. leprae* antigen 7 antibody activity was still present in the fractions containing IgM and IgG, again forming two distinct peaks, peak 1 and peak 2, as seen in Fig. 3. The position and the amount of *M. leprae* antigen 7 antibody activity was almost identical with the pattern seen after density gradient ultracentrifugation at pH 8.0. Similar results were obtained after density gradient ultracentrifugation of the LL serum pool. These findings indicated that the *M. leprae* antigen 7 antibody activity demonstrated in the fast sedimenting fractions after density gradient ultracentrifugation (denoted peak 1 in Fig. 1) did not consist of immune complexes.

Cord sera were fractionated by density gradient ultracentrifugation and the fast sedimenting fractions were tested in the RIA for possible *M. leprae* antigen 7 antibodies of IgM class. Fig. 4 shows a typical pattern of antibody activity against *M. leprae* antigen 7 in different fractions from both maternal and cord serum at delivery. After separation by density gradient ultracentrifugation, no antibody activity against *M. leprae* antigen 7 could be demonstrated in the cord serum sample in the rapidly sedimenting fractions, while the maternal serum had strong antibody activity in the fractions corresponding to IgM. Five additional cord-mother pairs were examined, and IgM antibodies against

M. leprae antigen 7 could not be dected in any of these cord sera. IgM does not cross the placenta, while IgG does. Therefore, the demonstration of *no* antibodies in rapidly sedimenting fractions of cord serum support the conclusion that the activity in these fractions of maternal sera was due to IgM antibodies towards *M. leprae* antigen 7.

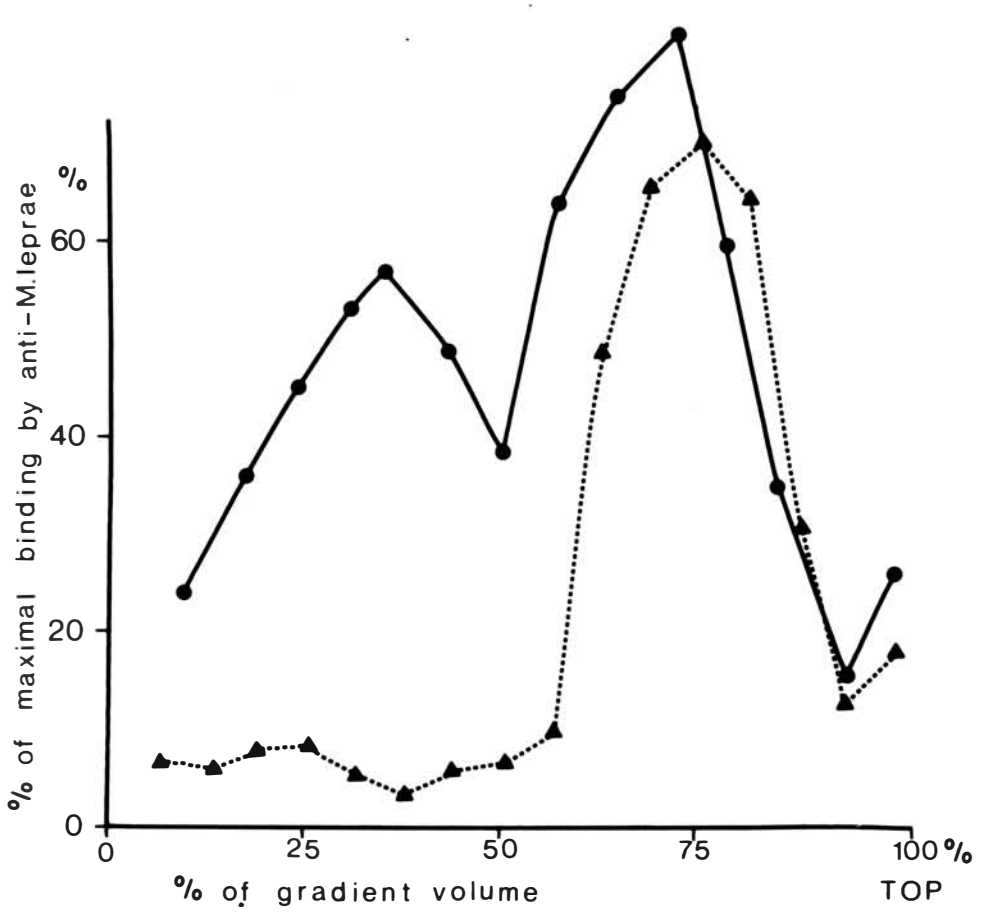

Figure 4. Antibody activity against *M. leprae* antigen 7 in fractions after density gradient ultracentrifugation of ▲---▲ baby's cord serum and ●——● the corresponding maternal serum taken at delivery.

Fig. 5a and 5b illustrate that different amounts of antibodies against *M. leprae* antigen 7 occurred in the IgM and the IgG class in four mothers with active lepromatous leprosy (Fig. 5a), in one mother with tuberculoid leprosy and in one mother who was a normal, non-leprosy control (Fig. 5b). These two figures showed that the sera from three out of four pateints with active leprosy contained antibodies of both the IgM and the IgG class against *M. leprae*

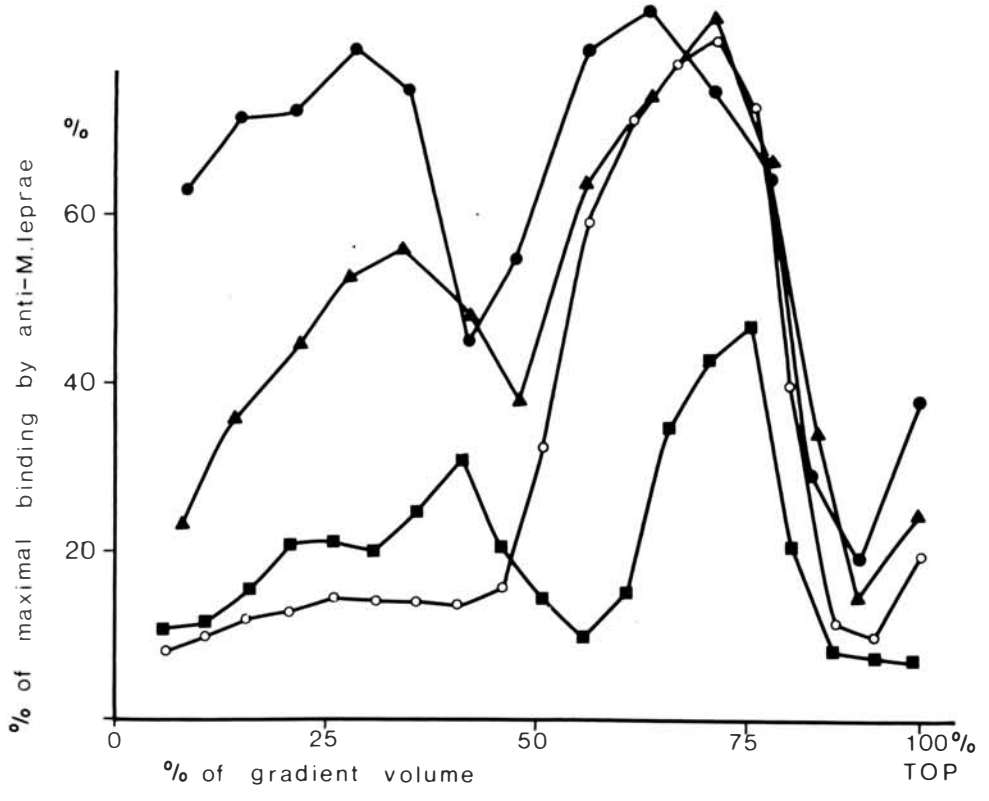

Figure 5a and b. Antibody activity against *M. leprae* antigen 7 in fractions after density gradient ultracentrifugation of: (a) 4 mothers suffering from active lepromatous leprosy, (b) 1 healthy mother ▲—▲, and 1 mother with tuberculoid leprosy ●—●.

antigen 7, while sera from the normal control and the patient with tuberculoid leprosy did not contain antibodies of this class against *M. leprae* antigen 7 detectable by the present technique.

Discussion

Patients with active lepromatous leprosy have more antibodies (both in concentration and specificity) than patients with tuberculoid leprosy or non-leprosy normal controls (Axelsen *et al.*, 1974;[6] Yoder *et al.*, 1979).[5] These antibodies have been considered mostly to be of the IgG class. Besides this no information is available regarding specific antibodies towards *M. leprae* in the different immunoglobulin classes.

IgM can be separated from IgG based on its faster sedimentation rate during density gradient ultracentrifugation of LL serum pool. Quantitation of IgM and

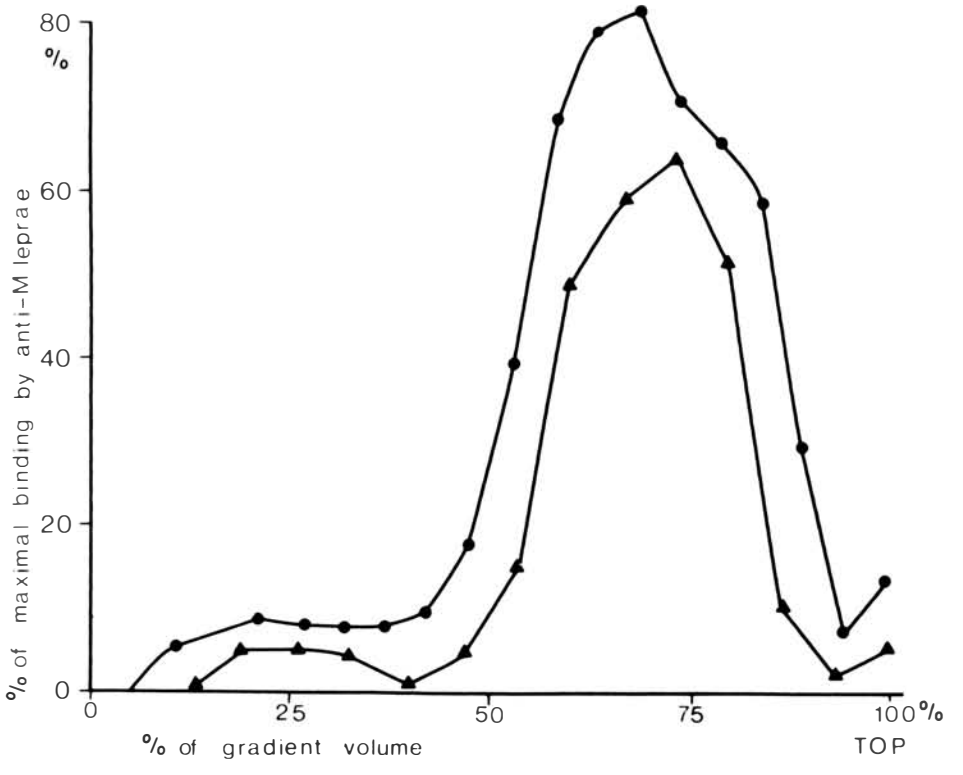

Figure 5a and b. Antibody activity against *M. leprae* antigen 7 in fractions after density gradient ultracentrifugation of: (a) 4 mothers suffering from active lepromatous leprosy, (b) 1 healthy mother ▲—▲, and 1 mother with tuberculoid leprosy ●—●.

IgG in the fractions showed peak of IgM concentration corresponding to the fractions denoted peak 1 in Fig. 1, while the peak of IgG concentration occurred in the slower sedimenting fractions corresponding to peak 2. The concentration of IgA was also quantitated in the fractions, and the distribution of IgA corresponded closely to that of IgG with maximum concentration in the same fraction as for IgG (data not shown).

M. leprae antigen 7 is one antigenic component of about 20 distinct antigenic components so far detected in *Mycobacterium leprae* by crossed immunoelectrophoresis. This preparation was labelled with ^{125}I, and was tested by crossed immunoelectrophoresis, and autoradiography and gel filtration. By these three techniques we could demonstrate that more than 95% of the radioactivity was localized to *M. leprae* antigen 7 (Melsom *et al.*, 1978).[4] We therefore used an isolated, defined labelled cell wall antigen which cross-reacts with several other mycobacteria.

RIA was carried out with labelled *M. leprae* antigen 7 on fractions obtained after density gradient ultracentrifugation of LL serum pool. Antibody activity

was found in the fractions with the highest concentration of IgM, peak 1, and in the fractions with IgG, peak 2. If any antibodies of IgA2 subclass against *M. leprae* antigen 7 are present in LL serum pool, these would be present in the same fractions as IgG, i.e. as part of peak 2.

After reduction and inactivation of IgM with 2-mercaptoethanol, almost no antibody activity towards *M. leprae* antigen 7 was found in the fraction corresponding to peak 1, while antibody activity towards *M. leprae* antigen 7 could be demonstrated in the fast sedimenting fractions after density gradient ultracentrifugation at pH 3.0, a procedure used to split IgG complexes whereas antibody activity due to IgM is not abolished.

We have demonstrated here antibodies towards *M. leprae* antigen 7 in both the IgM and the IgG classs. Thus several criteria used to distinguish IgM from IgG antibodies, i.e. presence in fast sedimenting fractions after density gradient ultracentrifugation, loss of activity after reduction, resistance to exposure to low pH, and lack of activity in cord blood have all been met in the present investigation.

It is still an open question if *M. leprae* bacilli or *M. leprae* antigens can cross the placenta. If the antibodies of the IgM class against *M. leprae* antigen(s) could be demonstrated in cord blood, this would strongly indicate that leprosy bacilli or antigen(s) from the bacilli cross the placenta. The present system used to demonstrate antibodies towards *M. leprae* antigen 7 in the IgM class, was therefore used to test if small amounts of IgM antibodies against this antigen are present in cord sera from babies of mothers with active lepromatous leprosy. But so far we have not been able to demonstrate IgM antibodies towards *M. leprae* antigen 7 in any of the cord sera we have tested. This can be due to our system being too insensitive. The protein A used as solid phase in this RIA system will only bind about 30% of the IgM present in adult sera (Harboe and Følling, 1974).[12] But these results could also indicate that *M. leprae* or *M. leprae* antigen 7 do not cross the placentae. A third possibility is that the foetus is unable to produce antibodies towards *M. leprae* antigen 7. To obtain more information on whether *M. leprae* or *M. leprae* antigens cross the placenta and affect the immune system of the foetus, we are presently developing other sensitive solid phase radio-immuno-assays for specific demonstration of anti-*M. leprae* antibodies in the IgG, IgA and IgM classes in cord serum.

Acknowledgements

This work was supported by grants from the Norwegian Research Council for Science and the Humanities, and by the Anders Jahre's Fund for the Promotion for Science. The leprosy bacilli used were supplied through the WHO Immunology of Leprosy (IMMLEP) Programme.

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Lepr Rev (1980) **51**, 137–148

In vivo effects of propranolol on some cellular and humoral immune functions in a group of patients with lepromatous leprosy

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Received for publication 20 October 1979

Summary Certain functions of blood neutrophils and lymphocytes were investigated at varying time intervals after the addition of propranolol to standard therapy in a group of patients with lepromatous leprosy. A control group of patients received standard therapy only. The leucocyte functions tested were neutrophil chemotaxis, phagocytosis and NBT reduction and lymphocyte mitogen induced transformation, leucocyte inhibitory factor production and number of spontaneous E, E and EAC rosettes. Serum immunoglobulins, complement components and total haemolytic complement were also measured in both groups. Over a 3-month period neutrophil chemotaxis, numbers of active-E and E rosettes, lymphocyte transformation and lymphokine production improved on standard therapy alone. However, although the propranolol group had the highest mean responses, there were no significant differences between the two groups of patients after one month and three months. Likewise there was no difference between the two groups with respect to other cellular or humoral investigations. Neutrophil chemotaxis appeared to be the best functional correlate of clinical improvement.

Introduction

Cell-mediated immune responses such as lymphocyte transformation to mitogens and antigens (Bullock and Fasal, 1971;[1] Rea and Levan, 1977;[2] Nath *et al*, 1977),[3] lymphokine production (Godal, 1972;[4] Talwar, 1972;[5] Myrvang, 1973)[6] and numbers of circulating T (Dwyer *et al.*, 1974;[7] Sher *et al.*, 1976)[8] and B (Mendes *et al.*, 1974;[9] Sher *et al.*, 1976)[8] lymphocytes are depressed in

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patients with lepromatous leprosy. Likewise phagocytic cell functions such as neutrophil motility (Bullock *et al.*, 1974;[10] Ward *et al.*, 1976;[11] Sher *et al.*, 1978)[12] and macrophage ingestion of *Mycobacterium leprae* (Barbieri and Correa, 1967;[13] Convit *et al.*, 1974)[14] have been reported to be abnormal in these patients.

Recently propranolol has been shown to possess immunostimulatory activity. This drug has been reported to increase normal and abnormal neutrophil motility *in vitro* (Anderson and Van Rensburg, 1978;[15] Anderson and Van Rensburg, 1979).[16] Buckley and McGregor (1978)[17] have reported that propranolol increased the number of survivors, decreased the duration of disease and increased the number of peritoneal exudate cells in rats which had been experimentally infected with type III pneumococci by increasing granulocyte adhesion. Furthermore propranolol can cause increased antibody synthesis in mice (Nakazawa *et al.*, 1976)[18] and rats (Benner *et al.*, 1968).[19]

We have previously reported (Anderson and Van Rensburg, 1979)[16] that the profile of effects of propranolol on leucocyte function *in vitro* is similar to that of levamisole. However the concentration of propranolol required to achieve stimulation of leucocyte function *in vitro* is approximately ten-fold less (Anderson and Van Rensburg, 1979).[16] For this reason a pilot study was undertaken to assess the immunologic status of a group of patients with lepromatous leprosy, also receiving standard therapy, before and after the administration of propranolol. No attempt was made to carry out a formalized clinical trial but changes in the clinical and histopathological picture were compared to the laboratory findings.

Patients

Twelve new untreated admissions (six borderline (BL), two sub-polar (LI) and four lepromatous (LL) were paired according to type of leprosy, age and sex (six males and six females). The classification was based on clinical and histopathological criteria of Ridley and Jopling (1966). All patients showed negative skin tests to lepromin. Patients in the control group received standard therapy of rifampicin (600 mg daily) for 6 weeks and dapsone (DDS, 100 mg daily) thereafter. The effects of treatment on immune functions were assessed by comparision of pre-treatment results with those obtained during treatment. Thus each patient served as his own control.

Propranolol

Each patient in the experimental group in addition to standard therapy received the beta-adrenoreceptor blockading agent propranolol in a fixed dose

of 40 mg t.i.d. over a twelve-week period. Clinical evaluation and immunological testing were done at the outset and during (one and three months) propranolol therapy. Histopathology on biopsy specimens was performed at the outset and after 3 months. They were assessed for cellular composition, bacterial index (BI) and the granularity index (GI) of the bacteria.

Cellular studies

NEUTROPHIL MOTILITY

Neutrophils were obtained from heparinized venous blood (5 units heparin/ml), washed twice with Hank's balanced salt solution (HBSS, Grand Island Biological Company, NY, USA) supplemented with 1 g/l of Hepes (Sigma, St Louis, Missouri, USA) to give a final pH of 7.2 and resuspended to a final concentration of 5×10^6/ml. Two leucoattractants were used in the study:

(a) Fresh pooled normal sera activated with 100 μg/ml of bacterial endotoxin (*E. coli:* 0127:B8 Difco, Detroit, Mich, USA).
(b) Endotoxin activated autologous serum. Both types of EAS were incubated for 30 min at 37°C followed by an eight-fold dilution with HBSS. Neutrophil motility was assessed as previously described (Anderson and Van Rensburg, 1979).[16] Chambers were incubated and the results expressed as the average number of cells reaching the lower surface of the 5 μ pore size Millipore after 3 hours incubation and expressed as an average for triplicate filters.

PHAGOCYTOSIS

This was assessed as previously described, by the ingestion of *Candida albicans* (Anderson and Van Rensburg, 1979).[16] Results are expressed as percentage *C. albicans* ingested in the presence of 10% fresh autologous serum.

NITRO BLUE TETRAZOLIUM REDUCTION

Tests of resting and stimulated (semi-quantitative) NBT reduction were performed according to the method of Sher *et al.* (1974).[21] The percentage of NBT (reduced) containing PMN was evaluated. For the resting test the normal result is $< 10\%$ positive PMN and in the stimulated test $> 90\%$.

LYMPHOCYTE TRANSFORMATION

Blood for studies of lymphocyte function was defibrinated and fractionated by density gradient centrifugation (Ficoll-sodium metrizoate) at 400 g for 25 min.

Mononuclear cells were washed twice in RPMI (Grand Island Biological Co, NY, USA). 2×10^5 cells (50 μl) were used in the assay which was done as previously described using PHA and CON A as the mitogens at concentrations of 25 and 50 μg/ml (Anderson *et al.*, 1979).[22]

LEUCOCYTE MIGRATION INHIBITION FACTOR (LIF) PRODUCTION

To 17 x 100 mm polypropylene culture tubes was added 0.5 ml mononuclear cell suspension (4×10^6/ml), 0.1 ml TC199 or 0.1 ml PHA (25 μg and 50 μg/ml) and the volume adjusted to 1 ml by the addition of serum supplemented TC199. The tubes were incubated at 37°C/96 hrs in a humidified atmosphere of 3% CO_2 in air. The cell free supernatant was removed and assayed for LIF according to the method of Weisbart and Mickey (1977).[23] Using human blood neutrophils as the indicator cells. Migration zones in the presence and absence of LIF containing supernatants were measured microscopically using a x 2.5 objective and a calibrated eyepiece graticule. The results are expressed as percentage inhibition of migration as calculated by comparison with the control system.

E AND EAC ROSETTES

Rosetting techniques were performed according to the method of Brain and Marston (1973).[24] Briefly, lymphocytes obtained by density gradient centrifugation were further purified by the elimination of contaminating phagocytic cells by iron adherence. The ratio of lymphocytes to E and EAC was 1:10. For EAC rosettes pooled human AB serum was used as a sub-lytic source of complement. Active E-rosettes were measured according to the method of Wybran and Fudenberg (1973).[25] The lymphocyte : sheep red blood cell ratio was 1:10. The mixture was centrifuged at 250 g/5 min before immediate counting of rosettes. A lymphocyte which had bound 3 or more red cells constituted a rosette.

Serological investigations

IMMUNOGLOBULINS AND COMPLEMENT COMPONENTS

The serum levels of IgG, IgA and IgM were determined by radial immunodiffusion using commercial plates and standards (Behring Institute). Serum C-3 and C-4 complement levels were assayed by rocket immunoelectrophoresis (Axelsen, Kroll, Weeke, 1973;[26] Laurell, 1972)[27] Results of immunoglobulin and complement estimations are expressed as mg/100 ml and mg/1000 ml respectively. Serum IgE levels were measured by radioimmunoassay (Phadebas

IgE test, Pharmacia diagnostics) and results expressed as IU/ml. The upper limit of normal is taken as 150 IU/ml. Serum CRP levels were measured by a semi-quantitative latex agglutination procedure, the normal value being $< 13.2\ \mu g/ml$. ASO antibodies were measured by inhibition of lysis of sheep red blood cells by streptolysin-O, and results expressed as the reciprocal of the titre (normal value 200).

Results

CALCULATION AND EXPRESSION OF RESULTS

Results are expressed as the mean value with standard error of the control and experimental groups for each investigation at each time interval tested. The results of each immunological test for control and experimental groups were compared by the Student's t test.

Neutrophil function

Results are shown in Table 1. Neutrophil chemotaxis was markedly impaired prior to the commencement of therapy and steadily increased throughout the three-month period, being most noticeable after the inclusion of dapsone. Although the increase in chemotactic responsiveness at one month and 3 months was greatest in the group receiving propranolol, the increase was not significant. The restoration of chemotatic responsiveness appeared to correlate with clinical improvement. Two patients in the control group and one in the experimental group showed no increase in chemotaxis throughout the trial period. These three also had less obvious clinical response to therapy. There was a slight but insignificant impairment of phagocytosis of *C. albicans* which normalized to a similar extent in both groups following therapy. Resting and stimulated NBT reduction was normal in both groups and remained unaffected with therapy.

Lymphocyte function

Results are shown in Table 2. Three patients in the control group and 3 in the experimental group showed reduced responsiveness to PHA (results $< 30{,}000$ cpm) and CON A (results $< 8{,}000$ cpm). The mean responsiveness to the mitogens increased to a similar extent in both groups following therapy, indicating that the improvement was due to standard therapy alone. A similar improvement in mitogen induced production of LIF, independent of propranolol supplementation, was also observed. Numbers of active-E, E and EAC rosettes were normal prior to therapy (with the exception of 2 with reduced

Table 1. Neutrophil chemotaxis to EAS, phagocytosis and nitro-blue tetrazolium reduction in a control group of patients with lepromatous leprosy and an experimental group who received propranolol in addition to standard therapy

Investigations	Control Group*			Experimental group†		
	Pre-treatment	1-month post-treatment	3 months post-treatment	Pre-treatment	1 month Post-treatment	3 months post-treatment
Chemotaxis to:						
a. Normal EAS (cells/HPF) (Normal value > 180 cells/HPF)‡	56 ± 19.7§	95 ± 45.0	131 ± 36.0	67 ± 25.5.	106 ± 16	232 ± 27.7
b. Autologous EAS (Cells/HPF) (Normal value > 180 cells/HPF)	26 ± 8.1	52 ± 31.0	129 ± 43.3	46 ± 15.2	73.1 ± 19.3	191 ± 26.8
Phagocytosis of C. albicans (% ingestion/25 min) (Normal value > 90%)	80 ± 6.4	82 ± 3.9	94 ± 1.6	86 ± 1.6	86 ± 2.7	95 ± 0.7
NBT Reduction						
a. Resting (Normal value < 10%)	10 ± 4.6	4.6 ± 1.9	8.7 ± 2.6	11 ± 3.0	8.7 ± 3.0	10.3 ± 3.8
b. Stimulated (Normal value > 90%)	97 ± 0.9	92 ± 1.1	95 ± 1.1	92 ± 0.5	95 ± 1.3	95 ± 1.1

*Receiving standard therapy only.

†Receiving standard therapy and propranolol 40 mg t.d.s.

‡The lower limit of the normal range of values shown here is taken as being one standard deviation below the mean of 100 control subjects.

§Results expressed as mean and standard error for six individuals.

Table 2. Lymphocyte mitogen induced transformation and relative percentages of active E, E and EAC rosetting cells in a control group of patients with lepromatous leprosy and an experimental group who received propranolol in addition to standard therapy

Investigation	Control Group*			Experimental group†		
	Pre-treatment	1 month post-treatment	3 months post-treatment	Pre-treatment	1 month post-treatment	3 months post-treatment
Lymphocyte transformation to:						
a. 25 μg/ml PHA (cpm)	26.264 ± 8.645‡	47.698 ± 19.483	45.482 ± 17.338	25.584 ± 5.746	59.904 ± 16.710	58.821 ± 20.980
b. 50 μg/ml PHA (cpm)	30.405 ± 8.323	45.216 ± 16.095	43.798 ± 15.125	23.386 ± 5.028	48.005 ± 11.592	50.994 ± 21.466
c. 25 μg/ml CON A (cpm)	7.639 ± 2.781	12.340 ± 8.042	18.462 ± 8.893	1.941 ± 612	12.255 ± 3.735	9.35 ± 2.010
d. 50 μg/ml CON A (cpm)	8.205 ± 4.494	14.934 ± 7.814	15.702 ± 7.979	4.199 ± 1.503	15.862 ± 5.230	12.156 ± 2.683
Rosetting cells						
a. Active E-rosettes (%)	47 ± 8.6	57 ± 3.0	54 ± 8.3	38 ± 10.0	46 ± 4.0	67 ± 8.1
b. E-rosettes (%)	62 ± 5.0	57 ± 4.5	66 ± 2.8	57 ± 7.1	60 ± 7.1	70 ± 4.1
c. EAC-rosettes (%)	34 ± 8.0	25 ± 8.0	28 ± 4.3	27 ± 6.5	27 ± 4.4	19 ± 3.5

*Receiving standard therapy only.

†Receiving standard therapy and propranolol 40 mg t.d.s.

‡Results expressed as mean and standard error for six individuals.

Table 3. Serum immunoglobulin and complement levels in a control group of patients with lepromatous leprosy and an experimental group who received propranolol in addition to standard therapy for a three-month period

Investigation	Control group*			Experimental group†		
	Pre-treatment	1 month post-treatment	3 months post-treatment	Pre-treatment	1 month post-treatment	3 months post-treatment
Serum IgG (g/l)	33.3 ± 3.3‡	33.3 ± 3.8	29.8 ± 4.0	33.8 ± 4.3	37.8 ± 4.3	31.3 ± 3.7
Serum IgA (g/l)	5.1 ± 1.1	5.6 ± 1.2	5.4 ± 1.1	5.4 ± 1.0	6.2 ± 1.0	5.9 ± 1.1
Serum IgM (g/l)	5.0 ± 1.1	4.3 ± 0.8	3.8 ± 0.6	5.0 ± 1.0	6.4 ± 1.4	4.1 ± 0.8
Serum IgE (IU/ml)	595 ± 248	485 ± 222	422 ± 780	1,700 ± 780	778 ± 276	1,350 ± 546
THC (CH50)	158 ± 8.1	162 ± 9.9	147 ± 6.6	166 ± 15.0	170 ± 20.0	145 ± 9.2
C'3 (mg/dl)	71 ± 7.1	66 ± 4.5	69 ± 7.0	65 ± 3.8	75 ± 8.4	66 ± 8.7
C'4 (mg/dl)	31 ± 4.9	36 ± 4.0	25 ± 3.0	25.3 ± 6.1	25.5 ± 4.4	28.6 ± 7.2

*Receiving standard therapy only

†Receiving standard therapy and propranolol 40 mg t.d.s.

‡Results expressed as mean and standard error for six individuals

numbers of EAC rosettes and with reduced numbers of E-rosettes in the control group) and remained unaltered throughout in both groups.

Serological studies

Serum immunoglobulins, including IgE, were elevated in both groups and remained increased to a similar extent throughout the 3-month period. Likewise levels of C3 and C4 and total haemolytic complement were normal at the outset and remained unaffected.

Histological results

There were no detectable differences between the control and experimental groups with regard to cellular composition of the biopsies, bacterial index and granularity index after 3 months of therapy.

Skin testing

All patients in each group remained anergic to lepromin after 3 months of therapy.

Patients

Using clinical criteria there appeared to be no differences between the two groups, although clinical improvement appeared to correlate with the extent of recovery of neutrophil chemotactic responsiveness. There were no adverse reactions to propranolol in the experimental group. The incidence of ENL was the same in both groups (2/6 in the control and 2/6 in the experimental groups).

Discussion

This study has confirmed previous reports that some patients with lepromatous leprosy have reduced lymphocyte transformation (Bullock and Fasal, 1971;[1] Rea and Levan, 1977;[2] Nath *et al.*, 1977)[3] and LIF production (Godal, 1972;[4] Talwar, 1972;[5] Myrvang, 1973)[6] to mitogens and depressed neutrophil migratory responses to leucoattractants (Bullock *et al.*, 1974;[10] Ward *et al.*, 1976;[11] Sher *et al.*, 1978).[12] However these functions of circulating leucocytes improved, and in almost all cases normalized, following 3 months of standard therapy with rifampicin and dapsone. The inclusion of propranolol, which has been reported to possess immunostimulatory properties, with standard therapy caused further improvement of neutrophil chemotactic responsiveness and

lymphocyte functions. However the magnitudes of the increases were not significant and did not correlate with any clinical, histopathological or bacteriological differences between the two groups. Likewise skin test unresponsiveness to lepromin was still evident in all members of both groups after the 3-month period.

These results indicate that immunostimulation with presently available agents may be of limited value in patients with lepromatous leprosy. In agreement with this contention is a recent report by Faber *et al.* (1979)[28] who were unable to detect any signifcant improvement in *in vitro* and *in vivo* immunological functions in a group of patients receiving transfer factor.

Of interest is the recovery of normal blood leucocyte function with standard therapy alone. Increased leucocyte responsiveness *in vitro* was most evident when dapsone was introduced to the therapeutic regime. Apart from its bacteriostatic effect (McCullough and Maren, 1973),[29] which may be directly related to improved leucocyte function by lessening the antigenic load and removing the source of serum inhibitors of leucotaxis (Sher *et al.*, 1978)[12] dapsone may have other modes of action (McDougall, 1979).[30] One possibility currently being investigated in this laboratory, is that dapsone *per se* possesses immunostimulatory activity, which may invalidate studies assessing the value of immunostimulants in patients with lepromatous leprosy.

Recovery of neutrophil chemotactic responsiveness appeared to correlate with clinical improvement since the three patients who did not recover normal neutrophil locomotion had the least clinical improvement. This apparent correlation between recovery of chemotaxis and clinical response to therapy is pesently being further investigated.

Although no striking immunological or clinical benefits were observed by the addition of propranolol to standard therapy in patients with lepromatous leprosy it is possible that the duration of the trial period was insufficient. However after 3 months of standard therapy ± propranolol blood neutrophil and lymphocyte functions had normalized in most patients, which indicates the likelihood that at this stage non-specific immunostimulation may be of little value.

Acknowledgement

The authors thank Professor IW Simson of the Department of Histopathology, Institute of Pathology, University of Pretoria, for interpretation of the biopsies.

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Lepr Rev (1980) **51**, 149–154

The incidence of disabilities in Hansen's disease after the commencement of chemotherapy

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Received for publication 28 November 1979

Summary Of 529 patients diagnosed as having Hansen's disease during the period 1 January 1971 to 31 December 1976 in the tropical twin island nation of Trinidad and Tobago, 473 (89%) were free of disabilities at the time of diagnosis. Of these, 335 (71%) were re-evaluated in 1978 in an attempt to determine the incidence of disabilities during the first few years of chemotherapy. Only two patients (0.6%) in this group were found to have developed disabilities. We concluded that disability occurs very infrequently in Trinidad after the diagnosis of Hansen's disease and the commencement of chemotherapy.

Introduction

One of the commonly expressed fears of patients who have Hansen's disease has been that, sooner or later, disabilities will develop. We could understand their concern, as we have seen many patients with disabilities. Yet, from a theoretical standpoint, it seemed that disabilities did not need to occur. In addition, from our observation of patients diagnosed in the 1970s, we rarely saw disabilities developing among them. With adequate treatment to kill the *Mycobacterium leprae*, and to suppress or rapidly reverse any inflammatory episodes such as acute neuritis, we felt that disabilities should be preventable. Minimal information is available on this in the literature.

After several years of observing that the occurrence of disabilities was uncommon among our patients who are on chemotherapy we decided to conduct a follow-up study on all patients diagnosed with Hansen's disease in Trinidad and Tobago during the years 1971 to 1976.

Our objectives were to find: (1) the incidence of disabilities among those who were free of disabilities at the time of diagnosis, (2) what changes occurred in those with disabilities at the time of diagnosis, and (3) what relationship

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there might be between regularity of treatment and the development of or the regression of disabilities. This paper deals primarily with the first objective.

Methods

From early 1971 detailed information was obtained and recorded at the time of diagnosis for each newly diagnosed patient with Hansen's disease. This included an evaluation by our physiotherapist. When disabilities were found, appropriate measurements were obtained and tests were performed to establish a baseline from which future changes could be measured.

During 1978 our physiotherapist re-evaluated as many patients as possible of those diagnosed from 1 January 1971 to 31 December 1976.

We chose 31 December 1976 as our cut-off date in order to provide a minimum of at least one year on chemotherapy before re-evaluating a patient's condition.

Patients were examined for loss of protective sensation in hands and feet, nasal collapse, lagophthalmos, visual deficit, clawing and contracture of fingers, loss of opposition of thumb, absorption of digits, claw toes, wrist drop, foot drop and plantar ulcers. The World Health Organization classification of disabilities using five grades was used. A separate sheet was used for the recording of each patient's findings.

Results

Of the 529 patients diagnosed as having Hansen's disease between 1 January 1971 and 31 December 1976, fifty-six (11%) initially had disabilities, leaving 473 patients (89%) free of disabilities at time of diagnosis.

Of these 473 disability free patients, 335 (71%) were re-examined in 1978.

Of the 335 patients who were re-examined in 1978, only 2 (0.6%) had developed any disabilities subsequent to the commencement of chemotherapy (see Table 1).

One of these was a female (identification No S-71-25), who was four and a half years old when diagnosed on 3 June 1971 with the dimorphous-tuberculoid (BT) type of Hansen's disease. On 12 July 1976 she was first noted to have non-tender left ulnar nerve enlargement, and by 11 October 1976 had mobile clawing of the left second to fifth fingers plus sensory deficit in the left fifth finger. Further deterioration in the function of all the lumbrical muscles was evident upon examination on 23 January 1978.

As measured by clinic attendance, her overall drug intake had been irregular (see Table 2).

The other 44 patients diagnosed in 1971 who were initially free of disabilities

Table 1. Disability status of Hansen's disease patients diagnosed in Trinidad and Tobago 1971–1976

Status	No	Per cent
Total diagnosed	529	(100)
With disabilities	56	(11)
Without diabilities	473	(89)
Not re-examined in 1978	138	(29)
Re-examined in 1978	335	(71)
Found without diabilities in 1978	333	(99.4)
Found with disabilities in 1978	2	(0.6)

Table 2. Regularity of anti-Hansen's chemotherapy intake in patient S-71-25 from 1971 to 1975*

Year	Regularity (%)
1971	87
1972	65
1973	83
1974	65
1975	25

*75% or greater is considered to be regular treatment (ie, the collection of 75% or more of prescribed drugs).

Table 3. Cohorts* of Patient S-71-25 Taking Anti-Hansen's Chemotherapy Regularly, 1971 to 1975:

Year	Number on regular treatment	Percent on regular treatment
1971	30	70
1972	26	60
1973	20	45
1974	18	40
1975	15	35

*Other Hansen's Disease patients diagnosed in 1971

and were re-examined in 1978 also had a poor record of treatment regularity (see Table 3).

Over the same five and a half year period only twelve of these 44 (27%) had been consistently regular in taking their treatment.

The other patient with a disability was a male (identification number D-76-65) who was sixty-seven years old when diagnosed on 17 November 1976 with the dimorphous (BB) type of Hansen's disease. At the time of diagnosis he had a non-tender moderately enlarged right ulnar nerve. On 14 January 1977

he was first noted to have slight motor weakness in muscles supplied by the right ulnar nerve, but no clawing. At this time he had ulnar pain. He was taking medication regularly during these first two months. 37 out of 59 (63%) other Hansen's disease patients also diagnosed in 1976 who were free of disabilities had taken treatment regularly during 1976.

Of these 138 patients who were not re-examined investigation revealed that 78 had been discharged from the clinics as cured, 32 could not be located, 19 had migrated and 9 had died (see Table 4).

Table 4. Disability-free patients not re-examined in 1978

Reason	No
Discharged	78
Lost	32
Emigration	19
Death	9
TOTAL:	138

By examining the records we found that none of the 78 discharged patients had disabilities at the time of their release. Nor did any of the 9 who died have any disabilities when last examined.

Only one of the emigrants developed a disability prior to leaving the country. This was a male (identification number M-73-24), who was 15 years old at the time of his diagnosis on 28 March 1973, and developed a weakness in dorsiflexion of his right foot in late May 1973. He had the dimorphous (BB) type of Hansen's disease, attended clinic irregularly and took medication only 50% of the time between diagnosis and the onset of this disability. No peripheral nerves were noted to have been enlarged or tender at the time of diagnosis. When he left the country in February 1977 he had a right footdrop (grade 2 disability). 79 per cent of his disability-free cohorts maintained regular chemotherapy during 1973.

Thus a total of three patients out of 473 (less than 1%) are known to have developed disabilities since the commencement of anti-leprosy chemotherapy. This is in sharp contrast to the 56 out of 529 patients (11%) who had disabilities prior to chemotherapy.

Discussion

Although the numbers are too small to be statistically significant, it is of interest that all 3 patients who developed disabilities were in the dimorphous (borderline) portion of the Hansen's disease spectrum.

Over this six-year period of time the number of newly diagnosed patients in

each part of the Hansen's disease spectrum were: indeterminate 20, tuberculoid 313, dimorphous 154 and lepromatous 42. Thus if patients in each type have the same probability of developing disabilities we would expect the majority of disabilities to develop in tuberculoid patients. Instead, all disabilities developed in dimorphous patients during the period under observation (see Table 5).

Table 5. Comparison of observed and expected incidence of disability by type of Hansen's disease among patients diagnosed in Trinidad and Tobago 1971–1976

Type	Observed	Expected
Indeterminate	0	0.1
Tuberculoid	0	1.8
Dimorphous	3	0.9
Lepromatous	0	0.2
TOTAL	3	3

It is also of interest that 2 of the 3 patients were irregular in taking their treatment prior to the development of disabilities. The one who was on regular treatment had neural involvement at the time of diagnosis as indicated by enlargement of the ulnar nerve.

Except for one patient who had evidence of neural involvement at the time of diagnosis and later developed a disability, none of the 143 patients who consistently took treatment regularly among the 335 examined in 1978 developed disabilities. However, only two patients developed disabilities out of the remaining 192 patients who were irregular in their drug intake.

With a significant proportion of those patients who were free of disabilities being irregular in taking treatment, one wonders why more disabilities did not occur. One possible explanation may be found in the treatment schedule of the 1970s when daily drug intake (Dapsone 50 mg) was commenced instead of the former 100 mg once to thrice per week. In 1978 we increased our standard dosage of Dapsone to 100 mg daily. Adequate blood levels of drugs are more likely to be maintained even when occasional doses are not taken when on a daily regimen than when on a less frequent schedule.

Two of the 3 patients who developed disabilities developed them within two months of the commencement of chemotherapy. One wonders whether there is a causal relationship, or if neuropathological changes were already occurring at the time of diagnosis which progressed in spite of chemotherapy. The 67 year old patient, in particular, seems to fit into this latter category.

On the basis of this study we have concluded that minimal disability (less than 1%) occurs in Hansen's disease during the first few years of chemotherapy.

Additional studies are necessary to clarify the various factors in chemotherapy that are responsible for preventing disabilities.

Acknowledgments

The authors wish to thank the Ministry of Health in Trinidad and Tobago for permission to publish this paper. We also thank Dr Felton Ross (American Leprosy Missions) for his valuable advice and encouragement, Mr Adrian Lambourne, Statistician (Caribbean Epidemiology Centre), for his helpful assistance in the presentation of our data and Miss Wendy Akal for her typing of the manuscript.

Lepr Rev (1980) **51**, 155–166

Disability in leprosy: a relevant measurement of progress in leprosy control

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Summary 931 patients have been detected in a Leprosy Control Project in Karnataka, India, giving a prevalence of 4.86/1000. 292 of these cases have disability and these are analysed in detail using the WHO Disability Index DI – 2. The effects of different forms of treatment on this Index are examined. It is suggested that incidence of disability is a more relevant measurement of the effectiveness of leprosy work than the incidence of cases. Secondary preventative measures are unlikely to prevent new cases whereas primary preventative measures for disability should affect the incidence of disability. This study forms the base line of a prospective study of the incidence of disability.

Introduction

It is well recognized that leprosy control is unlikely to be achieved using the current methods of secondary prevention (Meade, 1971).[1] The well-documented fact in some countries that quality of leprosy control has little effect on the number of new cases occuring (Davey, 1974)[2] after an initial fall, tends to have a depressing effect on field workers in leprosy control. In the light of these reports they feel they have been given an almost impossible task.

The vast amount of literature now appearing in journals and the press regarding a vaccine for leprosy increases this depression. Why should we struggle with very difficult work when an easier method is shortly to be produced? The fact that a vaccine will not shortly be available (Godal, 1978)[3] is not always pointed out clearly.

It is deformity which sets leprosy apart from other diseases (Brand, 1964)[4] and to the lay person leprosy means deformity (Scrinivasan and Dharmendra, 1978).[5] This is something we should use as a more relevant measurement of leprosy work until the day of primary prevention dawns. Our concern should be the occurrence of deformity rather than the occurrence of cases since leprosy is in a very real sense deformity.

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Information about the epidermiology of disability in leprosy is increasing (Chum *et al.*, 1970;[6] Cross, 1972[7] Karat *et al.*, 1970,[8] 1972;[8] 1975;[9] Hansan, 1977;[10] Bravo and Ratard, 1977).[11] The various studies have used different criteria for evaluating disability. The proposed disability index (Bechelli and Domingue,[2] 1971)[12] gives a method of evaluation for use in comparisons between different areas and from time to time. Most of these studies are prevalance studies although some give development and progress in treatment of disability.

This study sets out as a baseline to examine the prevalence of disability and the various factors effecting this and the general background details of leprosy in the area. Yearly assessments are planned to look at the incidence of disability as a more relevant criteria of the efficiency of leprosy work.

Methods

Survey of the general population was carried out in two Talukas (Rural) of Belgaum District, Karnataka in India, according to the guidelines for Leprosy Control Programme in India, in a target population of 233,581 (1971 census) located in 126 villages ranging from 75 to 18,950 population.

The programme was carried out by health education at individual, panchayat and village levels; survey by house to house examinations, school survey and household contact surveillance. The work was carried out over a 3-year period, 1976–79, by a team of 11 paramedical workers, one non-medical supervisor (NMS) and one medical officer. All trained in leprosy.

All cases detected were confirmed by the NMS or Medical Officer at the nearest clinic and at the same time disability assessment was performed by the physiotherapy technician in the form of Disability Index – (DI – 2) (Bechelli, *et al.* 1971).[12]

All patients were commenced on Dapsone therapy given at monthly intervals at 31 clinics.

For analysis of the various groups the standard measurements of percentage disabled and the the mean DI – 2 of the disabled patients have been used.

Results

ANALYSIS OF ALL DETECTED CASES

The population enumerated in house to house survey showed a 2.7% increase in the 1971 census figure (37.8% of the population was 14 years and under).

The gross percentage examination of the enumerated population was 80% and the variation with age and sex is recorded in Table 1. Since the population was not uniformly examined the 931 detected cases represent 75% and not

Table 1. Percentage of examination by age and sex

Age and sex groups	Male	Female	Male child	Female child	Total
Examination	67	82	88	90	80

80% of estimated cases because the group of highest prevalence (male adults) had the lowest examination rate. Since 28% of cases presented voluntarily, clearly more than 75% of total cases have been detected.

It is important to consider the distribution of all cases by age, sex type, means of detection and the various prevalence rates before analysing the disabilities. These details are recorded in Table 2. The gross prevalence rate was found to be 4.86 per thousand and the male adult, female adult and child prevalence rates were 8.89, 4.34 and 2.59 per 1000 respectively.

Table 2 shows that at the lepromatous end of the spectrum there is an increase in the percentage of adult males and voluntary cases which all have an important influence in the distribution of disability.

DISABILITIES AND SEX

The details of disabilities and sex are recorded in Tables 2, 3, 4 and 5. The percentage of female patients with disability (20%) is significantly less than that of male patients (38%) ($p < 0.05$). The mean DI for female patients is less than for male patients but the difference is not significant. The difference in the percentage disabled can be accounted for by the fact that the Borderline Lepromatous (BL) and Leprosmatous (LL) case have the greatest numbers of disabled patients and also the highest male/female ratio. Both sexes show rise in disability with age and the mean age of disabled patients is the same in both sexes.

Table 2. Analysis of detected cases by age, sex and type showing mean age and main methods of detection

	I	T	BT	BL	LL	Total
Male adult	45	174	96	38	118	471
Male child	55	52	11	–	2	120
Female adult	34	131	58	12	18	253
Female child	38	34	13	1	1	87
Total	172	391	178	51	139	931
Mean age in years	19.8	32.2	37.0	43.5	39.4	32.2
By general %						
house to house	84	73	66	61	36	68
Voluntary %	6	21	31	39	63	28
Other	10	6	3	–	1	4
Prevalence						
rates/1000	0.90	2.04	0.93	0.27	0.73	4.86
Sex ratio M/F	1.4	1.4	1.5	2.9	6.3	1.7

Table 3. Disabilities by sex and type

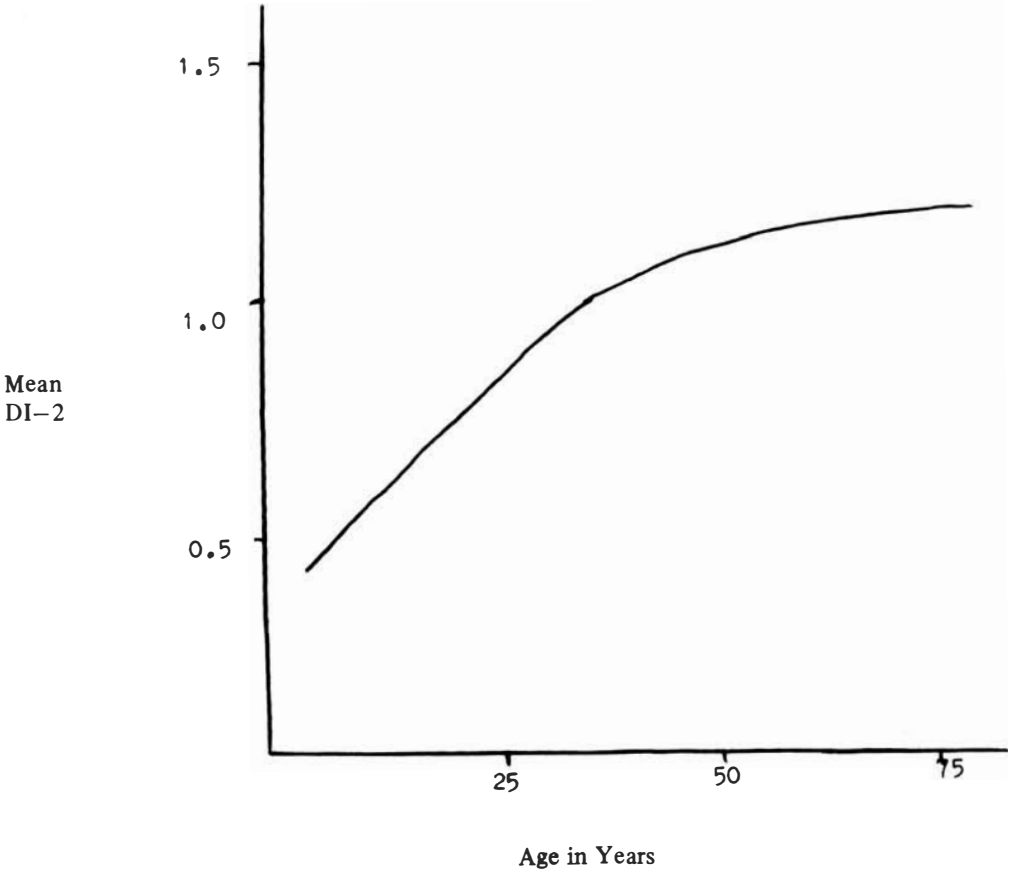
	Males				Females				Total			
	No of cases	No disabled	% disabled	Mean DI	No of cases	No disabled	% disabled	Mean DI	No of cases	No disabled	% disabled	Mean DI
I	100	0	0	0	72			–	172	–	–	–
T	226	48	21	0.8	165	21	13	0.9	391	69	18	0.8
BT	107	62	58	1.3	71	29	41	1.0	178	91	51	1.2
BL	38	27	71	1.2	13	10	77	1.4	51	37	73	1.3
LL	120	86	72	1.2	19	9	47	1.0	139	95	68	1.2
Total	591	223	38	1.2	340	69	20	1.0	931	292	31	1.1

DISABILITIES AND TYPE

Details of disabilities and type of leprosy is recorded in Tables 2, 3 and 5. The percentage of disabled cases varies with type, the highest being the BL and LL groups. The mean DI is least in the tuberculoid (TT) group. There is also a rise in the mean age of the groups from TT and LL. Type of leprosy is clearly a major factor in disability. The BL group has the highest percentage disabled and the highest mean DI.

DISABILITIES AND AGE

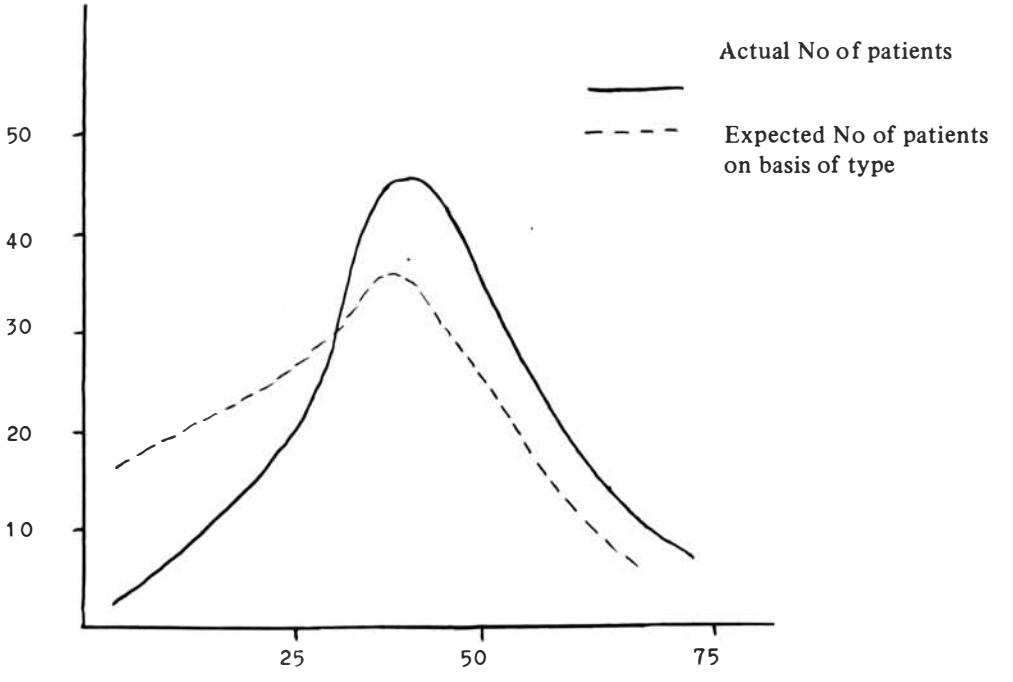
Details of disabilities and age are recorded in Tables 2, 4, 5 and Graphs 1 and 2. The mean age for all patients is 32.2 years and for the disabled patients it is 43.0 years. The average age increases towards lepromatous end with BL cases having the highest mean age. The percentage of disabled patients increases with age as seen in Table 4 as also does the mean DI. Graph 1 is of the mean DI against age.



Graph 1. Mean disability index – 2 against age

Table 4. Disabilities by sex and type

	Males				Females				Total			
	No of cases	No disabled	% disabled	Mean DI	No of cases	No disabled	% disabled	Mean DI	No of cases	No disabled	% disabled	Mean DI
0–4	3	–	–	–	6	1	17	0.5	9	1	11	0.5
5–14	117	5	4	0.4	81	4	5	0.5	198	0	5	0.4
15–24	88	18	20	0.7	41	6	15	1.3	129	24	19	0.8
25–34	93	32	34	1.1	53	8	15	0.9	146	40	27	1.0
35–44	109	62	57	1.3	58	13	22	1.1	167	75	45	1.3
45–54	115	64	56	1.2	52	19	37	1.0	167	83	50	1.2
55–64	40	32	64	1.3	37	14	38	1.3	87	46	53	1.3
65 +	16	10	63	1.2	12	4	33	1.2	28	14	50	1.1
Total	591	223	38	1.2	340	69	20	1.0	931	292	31	1.1



The actual number of patients lags behind the expected number of disabled patients standardized on the basis of type, showing that age affects disability independently from type of leprosy.

Graph 2. Number of disabled patients against age

Since the older age groups have less Indeterminate (I) and TT cases and more borderline and lepromatous, on the basis of classification alone an increase in disability with age would be expected. In Graph 2 each age group has been standardized for type of leprosy and the expected cases for each age group plotted. On the same graph the actual figures have been plotted and it is seen that age has an effect on disability apart from type.

Table 5. Mean age of disabled patients and of total patients by sex and type

	Male		Female		Total	
	Total	Disabled	Total	Disabled	Total	Disabled
I	18.7	–	21.4	–	19.8	–
T	30.5	41.9	34.5	43.7	32.2	42.4
BT	38.5	41.4	36.6	42.7	37.0	41.8
BL	45.2	46.1	38.6	43.0	43.5	45.2
LL	40.0	44.3	36.1	40.9	39.4	44.0
Total	32.1	43.2	32.4	42.8	32.2	43.0

The gap in the mean age of each classification group from the mean age of the disabled is largest for tuberculoid patients and very small for borderline and lepromatous.

ACTUAL DISABILITIES

The actual disabilities are recorded in Table 6. If it is accepted that anaestheasia and absorptions of hands and feet, stiff joints and blurring of vision are all irreversible then the revisible component amounts to 17.6% of the total disability.

The reversible components can be subdivided into those reversed by surgery such as mobile claw hand, claw toes, drop foot and lagophthalmos and those reversed by health education, MCR chappals and OPP Boots. Surgery accounts for 7.3% and health education to 10.3%.

The cases which may benefit from surgery were analysed individually for suitability (Andersen, 1974).[13] Out of all cases of foot drop and mobile claw hand only 16 were suitable, others being excluded because of positive smears, absorptions or age. Also claw toes not associated with foot drop were excluded. Out of the 16 patients, 6 have refused surgery because they are coping at their employment despite disability. Thus the realistic component reversible by surgery is only 1.2% of the total disability. Stiff joints may be reversed but these are not included.

The disability which can be corrected by health education includes injuries and ulcers of the hands and planter ulceration. Again 100% reversal is unrealistic

Table 6. Actual disabilities

Anaesthesia only	117 (40%)
Anaesthesia & deformity	175 (60%)
Total	292 (100%)

	Total	Bilateral
Hands		
Ulcers and injuries	16	5
Mobile claw hand	35	9
Slight absorption	53	30
Stiff joints	25	13
Severe absorption	9	3
Feet		
Tropic ulcers	60	20
Claw toes	12	5
Foot drop	13	2
Slight absorption	50	31
Severe absorption	7	2
Face		
Lagophthalmos	4	1
Blurring vision	2	1

Table 7. Relationship between disability and deformity (type wise)

	T	BT	BL	LL	Total
Disabled	69 (18%)	91 (51%)	37 (73%)	95 (68%)	292 (31%)
Deformity	42 (11%)	52 (32%)	23 (45%)	53 (38%)	175 (19%)
Ratio					
Deformity/Disability	0.61	0.57	0.62	0.56	0.60

and a large series shows up to 40% recurrence of ulceration despite health education, POP and use of MCR chappals. (Sderberg, 1970).[14] So that more realistically only 7.1% to total disability can be reversed by these methods.

Thus although 17.6% of all disability is potentially reversible, only 8.3% could be achieved realistically, if reconstructive surgery were available, health education, Physiotherapy, POP casts and MCR chappals.

DISABILITY AND DEFORMITY

The relationship between disability and deformity is recorded in Table 7. Sixty per cent of all disabled patients have deformity (altered shape) and this ratio does not vary with classification; being remarkedly constant.

DISABILITY AND MODE OF CASE DETECTION

The analysis of disability, mode of detection and type is set out in Table 8. Of those detected by house to house survey, 23% had disability whereas of those who reported voluntarily, 58% had disability. In the BL and LL groups, the percentage disabled did not vary with mode of detection whereas in the BT and TT there was marked variation.

Discussion

The leprosy disabilities in a leprosy control programme have been analysed using the WHO DI – 2 Index. This shows that 31% have some disability and mean DI for those disabled is 1.1. It has been shown that many factors influence the prevalence of disability and these factors have been analysed. Less female patients were disabled than male but the greatest M/F ratios are at the lepromatous end of the spectrum. Type of leprosy was a major factor in disability. Percentage disability and mean DI increased with age independently from type. Analysis of the actual disabilities showed that health education, etc, had a greater potential in reducing disability than reconstructive surgery.

The relationship between disability and deformity (altered shape) did not vary with type. Patients who presented voluntarily showed a much higher percentage of disabled than those found in house to house survey.

Table 8. Disabilities and the mode of detection

	House to house survey		Voluntary reporting		School survey		Household Contact survey		By all modes	
	No of cases	% Disabled	No of cases	% Disabled	No of cases	% Disabled	No of cases	% Disabled	No of cases	% Disabled
I	144	–	11	–	6	–	11	–	172	–
T	287	13	81	46	10	–	13	–	391	18
BT	118	40	56	73	3	33	1	–	178	51
BL	31	74	20	70	–	–	–	–	51	73
LL	50	76	88	65	–	–	1	–	139	68
Total	630	23	256	58	19	5	26	0	931	31

When analysing the rates of leprosy it is seen that the prevalence rate falls quite rapidly when a treatment programme is started mainly due to the reduction in duration of the disease, whereas the incidence rate is constant after an initial drop. This initial drop can be explained by low examination rates in the higher prevalence group, ie male adults which is gradually made up in subsequent survey; the keeping of suspects which on subsequent survey are identified as cases also produces this fall.

This study is the start of a prospective study looking at the prevalence and incidence rates of disability. Since it is disability which sets leprosy apart from other diseases and results in the major problems, disability rates may be a more important and relevant measure of the effectiveness of a leprosy detection and treatment programme than the number of actual cases. Leprosy control by detection and treatment of cases, ie secondary prevention, cannot be a very effective method of control and leads to despondency among field workers. It should be noted that disease arrested is not synomymous with disability arrested.

Disability control on the other hand is a method of primary prevention. Since a high risk group can be selected, ie those who have leprosy but no disability and disability prevented by treatment, health education, etc. It is suggested that the prevalence rate of disability will fall slowly as severely disabled patients become old and die; and that the incidence rates of disability will fall more rapidly as cases are detected and treated early and deterioration is prevented in established cases.

We suggest that analysis of disability prevalence and incidence rates is more relevant measure of a leprosy programme's effectiveness until the day of primary disease prevention eventually dawns.

Acknowledgements

This work was carried out in the Leprosy Mission Hospital in Belgaum. We are grateful to the team of 11 paramedical workers and the physiotherapy technician for their work and to Mr P T Edward for preparing the manuscript.

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Health education and leprosy

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Received for publication 14 October 1979.

Summary In the context of effective health education in leprosy, various theories from the behavioural sciences are reviewed. In a project carried our near Vellore in South India over a period of $1\frac{1}{2}$ years, the three main stages included information, motivation and action. The objectives were to make the patients come for early and regular treatment, to make the public willing to employ patients and not to avoid harmless contact with them, and to make patients take proper care of their hands and feet. The techniques employed are described and the results analysed – indicating a considerable improvement in knowledge, attitude and reported practice.

The aim of health education is to change people's behaviour in a way that is beneficial for their health. Merely giving information is seldom adequate to achieve this change in behaviour, and a learning experience is usually more effective. However this is difficult in leprosy because no quick results can be seen. Health education is based on the behavioural sciences – social psychology, sociology and anthropology, and applies insights from these sciences to bring about behaviour change. It is important to understand the beliefs of the people before starting to give health education, and here anthropological studies are of value. For example many people do not connect the patch with leprosy at all; they call it 'themal' in Tamil, and think it is the same as tinea, or they think it is a bite and do not take it seriously. The name 'leprosy' is reserved for the advanced disease with deformities. Thus to ask a person with an apparently harmless patch to attend a clinic where he will have to mix with advanced leprosy patients and to carry the same stigma as they do, is to make cooperation unnecessarily difficult. If patients with a patch were referred to a general clinic

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then the response might be much improved. Bhat (1978)[1] and colleagues in Karnataka told patients with a patch that their disease would develop into leprosy if they did not take treatment (which is true in terms of their concepts). In this way they were able to persuade patients to take treatment which they would not have agreed to if they had been told that they had leprosy.

Various theories from the behavioural sciences can be applied in health education. We have carried out a project in 5 panchayats near Vellore (Matthews, Jesudasan, Selvapandian and Benjamin 1979;[2] Matthews and Jesudasan 1978;[3] Jesudasan and Matthews 1978),[4] based mainly on the theories of Cartwright (1949)[5] and Lionberger (1960),[6] as well as a combination of several theories formulated by Matthews (1975);[7] see also Matthews, Benjamin, Samikkannu, Punithavithy and Palocaren (1977).[8] According to Cartwright's theory, it is necessary to change cognitive, motivational and action structure in order to change behaviour. To change cognitive structure, new information must be presented to the people in a form which is clear and acceptable to them. To change motivational structure the required behaviour must be seen as a path to some goal the person has. To provide the right action structure the person must have an easily available opportunity to carry out some specific action to produce the required behaviour.

Lionberger postulates five stages in the adoption of an innovation: 1. Awareness, 2. Interest, 3. Evaluation, 4. Trial, and 5. Adoption. For the first two stages the mass media can be effective, but for the later stages personal influence is more important, and for final adoption personal experience is what matters most.

According to Matthews' theory the probability that an action will be taken depends on the product of three factors:

1. The perceived probability that the action will lead to the goal (p),
2. The perceived importance of the goal (i),
3. The perceived effort required (e).

Since probability of taking action increases with decreasing effort, the third factor is $(1-e)$ and not e. The product is therefore $ip(1-e)$. Thus for advanced leprosy patients the goal of curing their disease may be of great importance to them (high i), but they may not believe in allopathic treatment (low p), and effort in taking treatment for so long may be great (high e). Therefore the product $ip(1-e)$ will be low and the action (taking treatment) may not be taken. For patients with only a patch, the problem will be even more difficult as already discussed. The effort (e) involved in taking treatment will be high due to the stigma and the importance of the goal will be low since the goal of curing the patch is not taken very seriously.

In the project carried out near Vellore (Matthews *et al.*, 1979),[2] there were three stages of education during $1\frac{1}{2}$ years – information, motivation and action corresponding to p, i, and $(1-e)$. The objectives were to make patients come

for early and regular treatment, to make the public willing to employ patients and not to avoid harmless contact with them, and to make patients take proper care of their hands and feet. An intermediate objective was to improve the knowledge of and attitude towards leprosy of patients and general public so as to achieve the required change in behaviour.

A knowledge, attitude and practice survey was carried out before and after the education was given, for evaluation. The detailed results of this survey before education was given have already been published (Matthews and Jesudasan 1978).[3] The information stage included training of staff, training camps for village leaders, public meetings, drama, film shows, leaflets, slides in

Table 1. Knowledge

	% Respondents			
	General public		Patients	
	Before	After	Before	After
Knowledge of:				
Patch as early sign	21	70	54	91
Cause due to germs	0	28	1	28
Complete cure possible	52	85	73	95
Not all types infectious	0	31	16	47
Incubation time more than 3 yrs	17	82	22	84
Prevention by treatment and check up	34	64	30	64
Injuries due to anaesthesia	Not asked		6	20
Patients without deformities can do hard work/all work	70	91	65	96
Patients with deformities can do light work	19	36	27	38

Table 2. Attitude

	General public		Patients	
	Before	After	Before	After
Mean score (%)	−12	43	3	50

cinemas, posters, and talks with flash cards to small groups. At the motivation stage various group meetings were held involving leaders, women, men, youth, teachers, etc. Leaders and regular patients were used to motivate those not taking regular treatment. Groups of patients were educated separately with emphasis on care of hands and feet. In the action stage attempts were made to remove barriers to action by reminding defaulters about the clinic, giving treatment by proxy for those who could not come, and in one village by running the clinic as a general skin clinic.

The results of the knowledge, attitude, practice survey after the three stages of education showed a considerable improvement in knowledge, attitude and

Table 3. Practice (patients only)

	% Respondents	
	Before	After
Go to hospital for dressing injury	69	95
Wear chappals always	17	34
Take care when cooking	9	36
Take advice from doctors, nurses, PMWs	21	79

reported practice. However some follow up is required to assess fully changes in practice. Some of the more important improvements are shown in Tables, 1, 2 and 3. The full results are given in the original report (Matthews *et al.*, 1979),[2] and the results before education in a previous publication (Matthews and Jesudasan 1978).[3] It can be seen from Tables 1–3 that there is a considerable effect. After the education many more respondents recognize the patch as an early sign of leprosy, and most know now that complete cure is possible. Before, practically none knew the cause of leprosy, now at least some know. Improvement is also seen in knowledge of infectivity, incubation time, prevention, cause of injuries, and patients' ability to work. Attitude (measured by Likert scale) has changed from being negative or only slightly postive to being much more strongly positive (Table 2.). After the education more patients say that they wear sandals always, go to hospital for dressing of injuries, take care when cooking, and take advice from doctors, nurses or paramedical workers.

The minimum resources required to produce such an effect in a population of about 200,000 would include, in addition to the usual staff of a leprosy control unit, one health educator, one social worker, and (for 6 months only) 2 projectionists and 2 projectors. The project would require a minimum of 2 years, preferably 3 years. A detailed plan has been made for such a project.

In another study (Matthews and Benjamin 1979),[9] it was found that even after many years of teaching individuals through home visits, little affect had been obtained, whereas the present project has produced considerable affect after only $1\frac{1}{2}$ years of education. In this other study the service area (population 7,560) was compared with a control area (population 7,260) in the same block. A knowledge, attitude and practice survey was carried out on a random sample in each area (sample sizes 289 and 284 in service and control areas respectively). Another similar survey in 2 different blocks was also carried out; the populations were 84,000 and 90,000 and sample sizes 1,528 and 1,580 in these two blocks. Attitudes, measured in a similar way to that used in the present study were 0.2% in the service area and 5.3% in the control area of the first block. In the other two blocks attitudes were −0.3% and 20.0%. These differences were not significant except for the

value of 20.0% which was attributed to a special leprosy project in that area carried out by SLRT Centre, Karigiri, for 13 years up to the date of the study. Knowledge of symptoms and cause was not significantly different in any of the areas, even in the Karigiri project area, and was similar to that found in the present study before the education. Symptoms mentioned were mostly deformities and ulcers, with only about 10% mentioning the patch. Cause was believed to be infection (by 8 to 13%), heredity or excessive sexual intercourse, with no significant differences between different areas.

Thus the comparison of the present study with this other one seems to indicate that the application of behavioural science principles does give a real improvement in results.

Acknowledgements

We are grateful to Dr V Benjamin, Professor and Head of the Department of Community Health for his guidance, also to Dr Jeyaprakash Muliyil and other staff of Rural Health Centre for their help. We also thank Mr P. Kuppusamy, Social Welfare Officer, Department of Orthopaedics and Leprosy Reconstructive Surgery for much help, as well as the field workers Mr Perumal Das, Miss Sirujunisa and Miss Stella Mary.

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Obituary

G NEWBERRY FOX, Esq, OBE

We recently received the following tribute from The Leprosy Mission in London –

11 December 1979

The death occurred today, at his home in Cumbria, of G. Newberry Fox, Esq, OBE, who until 1974 was General Secretary of The Leprosy Mission.

Born in Banbury, Oxfordshire, in 1906 and educated at Ayton School and Colchester Royal Grammar School, he was apprenticed as a millwright in Carlisle, became an assistant works engineer and, on his marriage in 1929, moved South to join his father-in-law's family building business.

His own father and his mother's father had left a business life to undertake Christian service and he believed that God was calling him into full-time Christian work. Coming as he did from a Quaker family, there did not appear to be any channel into which this call could be directed. However, as a young man, he had a great interest in the work of the then 'Mission to Lepers' and acted for a time as Honorary Treasurer of a supporting fellowship. This interest in the Mission's work was recognized when he was elected to the Council of the Mission in 1944 and he also served as Chairman of the England and Wales Council.

In 1958 Mr Fox was appointed Secretary for England and Wales and he believed that this was the fulfilment of the task which God had prepared for him in life. In 1962 a United Consultative Committee of the Mission met to consider future work and Mr Fox was appointed Promotional Secretary. With his active faith, business acumen, and great energy, his activities in this new field of work opened important doors of support in Europe and laid the foundation of the Mission's extensive work in many countries of that Continent. He also helped to foster closer relations between Headquarters staff and the supporting auxiliaries throughout the world.

In 1965 he was appointed as General Secretary of The Leprosy Mission, as it had become known. He and Mrs Fox journeyed far and wide on behalf of the Mission during a period of growth in the extent of the work. Mr Fox's work was recognized nationally when he was awarded the OBE in 1974. He retired in the same year and returned to live in the Lake District. Mrs Fox

pre-deceased her husband and Mr Fox remarried in 1978. He still retained an active interest in the work of The Leprosy Mission and was, at the time of his death, a Vice-President of the Mission.

His evangelical Christian faith, his advice, and his understanding will be sorely missed by former colleagues and the many friends who came into contact with him during his years of Christian service.

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Leprosy and the community

ACTION MEDEOR; DEUTSCHES MEDIKAMENTEN–HILFSWERK, D-4154 TOENISVORST 2, WEST GERMANY

This is a non-profit-making organization, set up in 1964, with the object of providing essential drugs at cost to the third world; it currently supplies over 1,700 stations in 82 different countries. The list of drugs runs to 125 items ranging from anaesthetics to water for injection, through antibacterials, antimalarials, dermatological preparations, fungicides, ophthalmological preparations, psychotherapeutic drugs, vitamins and minerals. The anti-leprotic section has dapsone tablets of 5, 10, 25, 50 and 100 mg strengths. Other 'leprosy drugs' are not stocked, partly on grounds of expense. Dexamethasone tablets 500 mg are available, as also injection of prednisolone 25 mg/ml. Cooperating organizations with Action Medeor include the following: Caritas, Fribourg; Caritas Internationalis, Rome; Catholic Relief Services, Geneva and New York; CIDSE, Coopération international pour le dévéloppement, Brussels; Christoffel Mission for the Blind, Bensheim; DAHW, German Aid Organization for the Lepers, Würzburg: German Institute for Medical Mission, Tübingen; German Red Cross, Bonn; Evangelical Mission Pharmacy, Tübingen; Circle of Friends Amazonas Hospital Albert Schweitzer, Bonn; Interchurch Medical Assistance, New York; Misereor Episcopal Aid Organization, Aix la Chapelle; Maltese Aid Service, Cologne; Medicus Mundi, Brussels; Mission Physical Institute, Würzburg; Salvation Army, London.

THE SECOND INTERNATIONAL WORKSHOP ON TRAINING OF LEPROSY WORKERS IN ASIA. BANGKOK, THAILAND, JANUARY 7–16TH, 1979. SASAKAWA MEMORIAL HEALTH FOUNDATIONS, TOKYO, JAPAN, AS CO-SPONSOR WITH THE MINISTRY OF PUBLIC HEALTH, THAILAND

As is now traditional with this Foundation, these Proceedings are beautifully presented in a 242-page paperback, including appendices and a list of participants from 8 different countries represented. The following specific educational objectives were defined at the outset:

(1) Identify the common problems of leprosy training programmes.
(2) State the basic principles of educational sciences which are applicable to leprosy control and leprology in its own setting, and:
    2.1 Develop a training programme (curriculum).
    2.2 Write educational objectives.
    2.3 Design appopriate teaching methods.
    2.4 Select and design teaching materials.
    2.5 Plan and conduct educational evaluation.
(3) Contribute training concepts in order to improve the training programmes generally and to improve the standards of teaching.
(4) Outline a reasonable plan for the development of his own institution in the training of leprosy workers.

The subject headings of the proceedings included: Training Programme Presentation and Programme Analysis; Principles of Learning; Motivation; Educational Objectives; Methods of Teaching; Media; Group Processes; Evaluation; Health Services and Manpower Development System; Planning Training; Managing Change; Evaluation of the Workshop Programme; Review and Conclusions, Impressions. This excellent account should be studied by all concerned with the training of leprosy workers, in any part of the world.

WHO; 'IN POINT OF FACT' NO 10/1980. BIOLOGICAL CONTROL OF DISEASE VECTORS

The opening paragraphs read as follows:

- WHO is encouraging and coordinating international research on the biological control of vectors as part of a special programme of research and training in tropical diseases. The programme is the outcome of a collective effort by many countries and international agencies to make better use of existing control methods, to train personnel and to develop research on these diseases.
- Specialized scientific working groups deal with the development of new control methods for each group of tropical diseases, in particular leprosy, malaria, filariasis, schistosomiasis, trypanosomiasis and leishmaniasis, or are responsible for activities, such as the biological control of vectors that cover all or most of these diseases.
- The objectives of the Working Group on the Biological Control of Vectors are to identify, evaluate and develop biological control agents for the safe and effective control of invertebrate vectors and intermediate hosts of human diseases, with special emphasis on bacteria, fungi, protozoa and nematodes.
- The Steering Committee of the Working Group has drawn up a plan of action for 1980 and 1981 in the light of the latest developments in biological control and the expected progress in research in this field.

- Research on the use of some entomopathogenic bacilli has become very promising and gives hope for the development of new biological insecticides. In particular, laboratory studies have confirmed the effectiveness of strain 1593 of *Bacillus sphaericus* against certain mosquito larvae and shown it to be possible to develop experimental formulations that are stable under local conditions.

WHO; *WHO FEATURES*, NOVEMBER 1979, NO 51, 'WATER AND DEVELOPMENT'

In a preface to an article by Paul Harison entitled 'Water and Development', which deals with the way in which the water/sanitation situation affects people in Africa, Asia and Latin America, this number of *WHO Features* refers to the aim of the United Nations system and Member States to provide water for all by the year 1990. The second page of the introduction is of considerable interest. It is entitled 'Disease related to deficiencies in water supply or sanitation' and is taken from a World Bank publicaton: 'Village Water Supply – Economics and Policy in Developing World', 1976, p. 32. It lists 34 diseases and leprosy is included under the heading 'Water-washed diseases' along with scabies, skin sepsis, yaws, lice and typhus, trachoma and conjunctivitis (and various intestinal infections). Information is also listed for the route of entry and exit of the pathogen; for leprosy the former is recorded as ? and the latter as ? nasal – the only question marks on the whole page.

WHO: PDT/DI/78.2. *DRUG INFORMATION*; APRIL–JUNE 1978; A BULLETIN DEVOTED TO INTERNATIONAL TRANSFER OF INFORMATION ON CURRENT DRUG PROBLEMS

Under the heading of 'Other recent regulatory decisions' 11 drugs or preparations are listed which include amiphenazone, the biguanides, bismuth preparations, chloramphenicol, and the chlorofluorocarbons. The section provides details of recent decisions taken to withdraw or restrict the use of specific drugs, particularly on grounds of safety, in a number of Member States. In the field of leprosy and tuberculosis, those who use isoniazid should note that it is included in this list, with the following statement:

'Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related and is increased with daily consumption of alcohol.'

'INDIA EMBARKS ON MULTIPURPOSE RESEARCH – 250,000 WORKERS INVOLVED'; FROM THE *INTERNATIONAL JOURNAL OF HEALTH EDUCATION*, VOL XXII, 1979/3, PAGES 143–9.

Some interesting paragraphs from this article by CR Krishnamurti on 'The active involvement of the people; exploring unconventional approaches' read as follows:

Over 80% of India's 650 million people are rural. They live in 580,000 villages, the population of each village ranging from 800 to 1,000. To provide health services for such a vast and dispersed population, 5,400 primary health centres and 40,000 sub-centres, have been developed and built in the last 27 years. Primary health centres each cover a population of approximately 100,000; they are staffed on average by two doctors and about 30 to 40 paramedical personnel including supervisors. Health education activities are provided by a health educator posted at the primary health centre.

Until about five years ago, referral facilities of a limited order were available at sub-divisional and district hospitals. The paramedical personnel at the primary health centres were rendering a variety of uni-purpose services as part of several vertical programmes of disease control. The personnel available at a primary health centre was insufficient to provide basic services, let alone health education and the like.

In 1974, on the recommendations of a special committee, a decision was taken (a) that all uni-purpose paramedical workers belonging to various vertical programmes would follow suitable training and become multi-purpose workers, and (b) that the total number of such workers would be gradually increased so as to provide one male and one female worker per 5,000 population, with suitable adjustments for hilly terrains, desert areas, isolated hamlets, etc. This decision involved enormous effort in solving administrative, financial and other problems.

Firstly, the exisiting 100,000 male uni-purpose workers, 50,000 female auxiliary nurse-midwives and 40,000 supervisors had all to be retrained in the multi-purpose philosophy and approach without seriously disturbing the ongoing activities. This training programme started in earnest in 1975 and is expected to be completed by 1981–82. The process of group learning – each uni-purpose worker transferring his skills and knowledge to the others – and the development of the concept of team approach have been the hall-marks of this training.

The key persons who have taken leading roles at field level have been the doctors at the primary health centres and the health educators who, after assessing the needs of the community in which they work, teach the other paramedical workers the social, educational, economic, cultural and other factors which influence health status and activities within the primary health centre. The training institutions at the national and state levels, which had

earlier been giving stereotyped training, had to adapt themselves to the new approach. I am proud to say that health educators have taken a significant lead in faithfully implementing this decision.

WHO; PRESS RELEASE WHO/1 OF 4 JANUARY 1980. 'TUBERCULOSIS EXPERTS MEET TO DISCUSS LACK OF PROTECTION OF BCG VACCINES IN TRIAL'

The opening paragraphs read:

The World Health Organization will bring together tuberculosis experts in two meetings to examine the implications of a large-scale trial that has shown BCG vaccination as affording no protection against lung tuberculosis in the south of India.

The trial was launched in 1971. First findings, compiled seven and a half years later, have been published in the current issue of WHO's *Bulletin* (Vol 57, No 5, 1979), as well as in the *Indian Journal of Medical Research*.

Though exact dates have yet to be set, one meeting is tentatively scheduled for April and a second for June to address questions raised by the trial. In elaborating on results, WHO experts emphasize that, while surprising, they 'must not be interpreted as indicating that BCG vaccination is useless everywhere'.

A scientific group will be asked to advise on further research, and a study group will be requested to recommend policies for vaccination programmes now under way.

Some 260,000 individuals above the age of one month were covered by the Indian trial, which was aimed at preventing lung tuberculosis in the population of 209 villages as well as in a town in a district of Chingleput, west of Madras.

The questions raised in the Press Release are as follows:

Were there procedural flaws?
Were the BCG vaccines used of adequate potency?
Could other factors have played a role?
Should BCG vaccination be stopped?

(A leading article in *the Lancet*, London, 12 January 1980, entitled 'BCG; Bad News from India', discusses some of the implications in greater detail.)

Lepr Rev (1980) **51**, 181–187

Field Workers Forum

We gratefully acknowledge the *WHO Chronicle*, Vol 33, No 9, September 1979, for the following article.

LABORATORY SERVICES AT PRIMARY HEALTH CARE LEVEL

WHO's programme of health technology relating to primary health care and rural development* includes collaboration with national health authorities in establishing laboratory services that are appropriate, inexpensive, acceptable and easily performed by laboratory personnel at the peripheral level. In that connexion, WHO has prepared a 20-page document 'Laboratory Services at Primary Health Care Level'† which is summarized below.

In many developing countries, primary health care is organized on four levels.

(1) At village level, health care is provided by a village health worker, often monitored by a village health committee, and technically supported by the next higher echelon of the health care system. Activities include the recognition, control and, where possible, treatment of communicable diseases, child and maternal welfare, nutrition and hygiene.
(2) Health work in a dispensary or subhealth centre, health post or clinic which may serve several villages and be staffed by a team of two or three health workers.
(3) A health centre providing support services and forming part of the referral system for the village and dispensary health workers. It might serve a population of 5,000 to 10,000 (or even much more) and be staffed by a team of four or more.
(4) The primary level hospital receives patients referred to it for medical attention including minor surgery and obstretrical surveillance, and provides technical and logistic support to the health centre team. It may also provide training for workers at lower levels. In some countries it is more developed and is considered as being at intermediate level.

In most developing countries, a laboratory service will usually exist only at

*See also resolution WHA29.74 in the *Handbook of Resolutions and Decisions*, Vol. II (3rd ed.), 1979, pp. 32–3.

†Copies of this document (LAB/79.1) are available in limited quantities. Requests should be sent to Health Laboratory Technology, World Health Organization, 1211 Geneva 27, Switzerland.

the primary level hospital. This is in accordance with the general policy of the majority of such countries, which is to develop health services at the central level and rarely at the periphery. Only recently have some countries such as Indonesia, Malaysia, the Sudan and the United Republic of Cameroon begun to establish laboratories in health centres.

Peripheral laboratories are generally manned by persons who have had only a short period of training. Technical supervision and guidance, quality control, proficiency testing, and provision of reagents and equipment should be the responsibility of the central or regional health laboratory. Quality control is essential for achieving consistently reliable laboratory results. At primary health care level its methodology should be very simple and adapted to local possibilities and resources. Direct supervision through periodical visits by senior laboratory staff is the most efficient method of supervision.

The primary level hospital laboratory might also participate in a more elaborate programme of quality control organized by the central laboratory. Apart from internal quality control based on good general laboratory practice with regular checkings of apparatus and reagents, the provision of control specimens by the central laboratory as part of a countrywide quality control programme would be something to aim at.

The health centre laboratory

The main functions of a health centre are to serve as a facility for patients referred from the dispensaries or the village health workers for screening purposes, for the delivery of preventive services and for antenatal and postnatal care including family planning, nutritional advice and health education. Administratively it is linked to the primary level hospital. It is staffed by a team including a medical assistant, a fully-qualified nurse, a midwife and two or three auxiliary personnel. It may have a few beds for observation of patients until referral to the hospital, if necessary.

The establishment of a laboratory in a health centre is justified because it can improve the quality and efficiency of primary health care. It can provide support to the health worker when the disease is difficult to diagnose clinically. A correct and early diagnosis will ensure the most suitable treatment for the patient, and in many cases the need for future hospitalization may be avoided, thus reducing the cost of health care delivery. Laboratory support can also help in the decision whether to refer a patient to the hospital.

The health centre laboratory will be of the type of an integrated laboratory performing both clinical and public health activities, although at a very simple level. It can nevertheless play a determinant role in the diagnosis of many common diseases in developing countries such as the following:

1. Parasitic diseases diagnosed by direct microscopic examination or after staining: malaria, filariasis (including onchocerciasis), trypanosomiasis, schistosomiasis, vaginal trichomoniasis, and amoebiasis, ancylostomiasis and other parasites diagnosed in stools.
2. Bacterial disease diagnosed by microscopic examination after staining: tuberculosis, leprosy, gonococcal infections, and meningococcal and pneumococcal meningitis.
3. Other conditions such as anaemia, diabetes and eclampsia.

According to the UNICEF Price List (UNIPAC) for 1978, the estimate of investment cost in equipment for this category of laboratory ranges from US $650 to US $750. The annual operational cost involved with provision of reagents and glassware is approximately US $100 to US $150 on the basis of 500–800 tests per month. As a laboratory assistant's skill will be sufficient at this level, the salary cost will be comparatively low; it is estimated that one laboratory assistant per 600–800 tests per month is necessary.

From the above, it can be seen that the cost of the establishment of a laboratory in a health centre is modest when related to the large benefits it can provide.

The health centre laboratory should be staffed by a trained laboratory assistant who should be part of the health centre team and be able to assist in other health activities when there is insufficient laboratory work. He should receive technical and logistic support and supervision from the nearest laboratory of higher level.

The main functions of this laboratory assistant are:

(a) to perform all simple routine analyses and direct microscopy in parasitology, bacteriology, haematology and chemistry (urine and spinal fluid) following written instructions;
(b) to collect and dispatch biological samples;
(c) to keep a record of expended material, chemical reagents and others and to order a new stock: and
(d) to prepare a monthly report of activities.

Essential laboratory tests for use in the health centre

Table 1 gives a list of essential tests which are the minimum that a laboratory should perform at the health centre level; these tests require very simple equipment and reagents.

In some countries, reagent test strips and kits are being used, e.g., in urinanalysis. Because of their cost and the problems related to their use in conditions of high temperature and humidity, a careful study should be made before introducing them in the laboratory.

Table 1. Essential tests and their methods suitable for a health centre laboratory

Essential tests	Method
Blood	
Haemoglobin	Comparator
White cell count	Counting chamber
Examination of a film for cell morphology	Stained film
Erythrocyte sedimentation rate	Westergren method
Parasites	Direct and Romanowsky stained preparations
Urine	
Protein	Sulphosalicylic acid method
Glucose	Benedict's method
Sediment for cells, casts, parasites	Direct microscopy
Sputum	
Identification of *Mycobacterium tuberculosis*	Ziehl-Neelsen stained smear
Stools	
Protozoa and ova	Direct saline and iodine preparation
Skin	
Identification of *Mycobacterium leprae*	Modified Ziehl-Neelsen stained smears
Test for *Onchocerciasis volvulus* microfilariae	Direct wet preparation
Pus and exudates	
Bacteria	Gram-stained smear, especially for gonococci

Laboratory services in a primary level hospital

In many countries, the primary level hospital corresponds to a district hospital. It generally has between 30 and 150 beds and covers a population of between 30,000 and 100,000. These figures may be widely modified by geographical conditions and concentrations of the population served. It is designed to deal with major health problems and serves as a referral centre for the peripheral health services. It should in turn refer very complicated cases and those requiring more precise diagnosis to a higher service echelon.

The primary level hospital will comprise an outpatient and an inpatient department. The former has similar functions to those of the health centre, while the latter has activities in general medicine, general surgery including surgical emergencies, and obstetrics including surgery for the prevention and treatment of complications. A laboratory and an elementary X-ray unit will be needed to support these activities.

The laboratory of the primary level hospital should have at least one qualified laboratory technician, and two or, if possible, more assistants.

The basic functions of the laboratory technician will be:

(a) to perform all routine and some special laboratory procedures as might be required by the hospital staff;
(b) to collect and dispatch specimens;
(c) to assist in the training and technical supervision of laboratory assistants and any other subordinate personnel;
(d) to prepare and list reagents;
(e) to maintain the laboratory equipment; and
(f) to prepare a monthly report of activities.

This laboratory should be part of the laboratory service network and be closely linked to the nearest regional or provincial hospital, i.e., higher level laboratory. From this level, it will receive technical advice and supervision and necessary laboratory supplies, including reagents which are ready for use. It will concentrate on individual tests and analyses to assist in the diagnosis and treatment of patients, but it should also be used as a public health laboratory for epidemiological control. The range of tests to be undertaken will include all those recommended for the health centre laboratory plus some basic tests in clinical chemistry, haematology, bacteriology and parasitology which are important for clinical and public health purposes at the peripheral level. Examples of tests of public health importance that are not directly related to hospital patient care are water testing (for chlorine and nitrate, which may be done by the sanitarian and not by the laboratory worker himself) and microbiological tests needed in controlling epidemics.

In many developing countries, bacteriological culture is not yet included in the duties of the primary level hospital laboratory. This omission is due partly to the cost and difficulty of obtaining equipment and reagents and partly to the technical difficulties. However, in view of the importance of communicable diseases at this level, every effort should be made to establish some basic culturing facilities, including those for performing coliform tests in water. If culture media, already prepared for use in simplified techniques,* are regularly supplied by the central laboratory, many of the technical difficulties can be overcome.

The WHO document ('Laboratory services at primary health care level', section 2.1, pages 8–9) lists 42 tests that should be performed at the primary level hospital laboratory. Lists of the equipment and reagents required respectively for health centre laboratories and for primary level hospital laboratories are given in Annexes I and II to that document, while Annex III

*An example of such simplified technology is given in a WHO document (BAC/78.2, LAB/78.2), 'Simplified procedures for the isolation and identification of enteric pathogenic bacteria', a revised edition of which will shortly be available from Health Laboratory Technology.

lists supplementary tests, equipment and reagents that may be needed at both levels to meet priority health needs of the community.

Collection and dispatch of laboratory specimens

In order that the benefits of more extensive laboratory facilities may be made available to the rural population, a reliable system of collection and transport of specimens must be established. This is primarily the responsibility of the laboratory worker, but where the system is extended to the dispensary or even to the village levels, other health workers could collect and dispatch specimens if specifically trained to do so.

It is the responsibility of the referral laboratory to supply the necessary containers to be used, as well as pertinent information on collection methods. In some countries these are directly provided from the central laboratory as part of a general programme of standardization of laboratory technology.

Training of laboratory workers

Laboratory workers at the primary health care level should receive an adequate training that enables them to perform their duties with a sense of responsibility. This implies not only practical competence but also a basic understanding of the clinical purpose of the tests performed and an appreciation of the role of the laboratory in the health service. They are part of the health team, and must collaborate harmoniously with the other members of the team.

They must be able to perform a range of tests in the fields of haematology, biochemistry and microbiology. In establishing a syllabus for training laboratory workers, attention should be given to actual health needs and available resources in the country, and to the definition of educational objectives. An indiscriminate adoption of syllabuses as used in developed countries should be avoided.

The health centre laboratory assistant should if possible come from the region in which he is to work. He should have from six to eight years of general education and a training of 6–12 months in the nearest district or regional hospital where facilities are available.* His training should be given by senior laboratory technicians with experience in teaching and the use of audiovisual material. As part of his formal course, the laboratory assistant should receive

*WHO is publishing a 'Manual of basic techniques for a health laboratory' giving detailed descriptions of most of the laboratory techniques that a laboratory assistant should know. WHO Technical Report Series, No. 345, 1966, & No 491, 1972, give more detailed information on the training of laboratory staff.

in-service training under supervision, and his supervisor should visit the place where he is to work in order to evaluate the facilities available. His supervisor should also visit the health centre regularly to give technical help and support to the laboratory assistant in his work.

The training of hospital laboratory technicians should be of two to three years' duration according to the general education of the student, which should preferably be 10–12 years of total schooling. The training should cover the most important laboratory techniques with a strong emphasis on practical work, and should take place in an organized institution. It should also include enough theoretical knowledge to enable the student to understand the basic principles of laboratory technology. In the final year of his training, the laboratory technician should spend at least three months in in-service training. He may also spend some time in a health centre laboratory to become acquainted with conditions in rural areas. This would also help to maintain the standard of work at the health centre, and provide the technician with some experience of work supervision at that level.

The laboratory technician should realize that he is a member of the hospital team with responsibility for integrating his work into the total activity of the hospital.

Lepr Rev (1980) **51**, 189–194

News and Notes

DR RUTH PFAU, MD, APPOINTMENT AS FEDERAL ADVISOR FOR LEPROSY TO THE GOVERNMENT OF PAKISTAN

Dr Ruth Pfau, MD Germany, was born on 9 September 1929 in Leipzig, and did her medical studies in what is now called the Eastern Part of Germany. After joining the Order of the Daughters of the Heart of Mary, whose Mother House is in Paris, she was on her way to India. She stayed for a while in Karachi and visited the Marie Adelaide 'hut' Leprosy Clinic, run by her Congregation, in the 'Beggar Colony' off McLeod Road. From the 'hut' has grown the main hospital with 70 beds and large OPD facilities, with 6 sub-centres and a home for crippled patients in Karachi. Present total case load is 12,000. She started the first Leprosy Technicians Course in 1965, and the institute has completed 11 courses, and 125 technicians have been trained both for the Government and private agencies. Dr Pfau, in search of the index cases, has travelled to every hill and valley of Pakistan. Since she has established leprosy services in nearly all the provinces in Pakistan, she has been decorated last year with the Hilal-e-Imtiaz, which is the highest Pakistani Civilian Award in the country, and just recently she has been appointed the Federal Adviser for Leprosy to the Ministry of Health, Government of Pakistan.

JAPAN HONOURS DR STANLEY BROWNE

At an impressive ceremony held in Tokyo recently, which was attended by Prince and Princess Hitachi and many government and civil dignitaries, the 'Special Appreciation Prize' was presented to Dr Stanley Browne, CMG, OBE, by the Nihon Kensho-Kai, a Japanese Foundation, for his outstanding work for leprosy sufferers throughout the world. In the absence of Dr Browne, a representative of the British Council received the prize on his behalf. The Prize consists of a beautiful hand-printed scroll and a cheque.

Dr Browne is the first non-Japanese to receive this prize, which is the highest accolade in the gift of the Japanese Foundation.

ILEP; 33rd MEETING OF THE MEDICAL COMMISSION, BRUSSELS, 13 DECEMBER 1979

This meeting was attended by the following: Dr S G Browne, Dr A Cap (Vice-President), Professor M Harboe, Professor M Lechat, Dr D L Leiker, Professor K F Schaller (President), Dr J. Terencio de las Aguas, Dr Felton Ross, Dr Yo Yuasa and Dr A C McDougall (Rapporteur). Mr Van den Wijngaert, General Secretary, was present during the morning session. Some of the more important items on a day-long agenda included: (1) new ILEP Guidelines for the Campaign against Leprosy. The last issue was in 1976 and it was considered essential to up-date this document in the light of new developments, especially in the matter of treatment; (2) a discussion of future ILEP strategy, with particular attention to what is being achieved with the present expenditure and the possibility of establishing survey teams for the collection of more data on the effectiveness of leprosy control programmes; (3) the assistance of UNICEF to leprosy control programmes; (4) Ethical Guidelines for organizations and individuals raising funds for use on behalf of leprosy sufferers; (5) a questionnaire on clofazimine (Lamprene; B663) from CIBA-GEIGY in Switzerland, asking for cooperation in the matter of obtaining accurate information on the tolerability of this drug, in as many patients as possible; (6) applications for advice or financial support on research projects from medical or scientific workers; (7) 12th International Congress of Leprosy, New Delhi, November 1983 – to which ILEP already has offered very considerable financial support.

The 23rd Working Session of ILEP/13th General Assembly of ILEP will be held in London, at the Strand Palace Hotel, London WC2R GJJ, from Tuesday 17 June to Sunday 22 June, the meeting of the Medical Committee being on Thursday 19 June.

TWO NEW PUBLICATIONS (TRANSLATIONS) IN PORTUGUESE

(1) Memorando Sobre o Controle da Hanseniase. Stnaley G. Browne.
(2) A Organizaçao Mundial de Saūde e A Hansenias. 5° Relatōrio do Comitê Tecnico em Hanseniāse.

(1) This is a translation of the joint OXFAM–LEPRA–The Leprosy Mission booklet, *Memorandum on Leprosy Control.* A few copies of this Portuguese version are available in the UK from OXFAM (274 Banbury Road, Oxford OX2 7DZ). In Brazil they can be obtained on application to OXFAM, Caixa Postal 1987, 5000, RECIFE, PE, or CERPHA, Caixa Postal 24046, 20000, Rio de Janeiro, RJ.
(2) This is a translation of the *Fifth Report of the WHO Expert Committee on Leprosy, Technical Report Series 607, WHO, Geneva, 1977.* Copies are available in Brazil from the two addresses given above.

'ANALYSIS OF RESEARCH NEEDS AND PRIORITIES IN DERMATOLOGY', *THE JOURNAL OF INVESTIGATIVE DERMATOLOGY:* SUPPLEMENTAL ISSUE; VOL 73/ NO 5, NOVEMBER 1979, PART II

This supplement issue of the JID (which is the Official Journal of the Society of Investigative Dermatology, Inc, and the European Society for Dermatological Research) extends to over 100 pages and covers the whole subject of dermatology in America under the following headings: Prevalence, Severity and cost of dermatological diseases; Psoriasis; Eczematous and immunological diseases; Acne; Malignant and benign neoplasms of the skin; Infections and infestations; Birth defects and genetic disorders; Dermatological needs in drugs and instrumentation; Malignant melanoma and vitiligo; Pruritus, pain and sweating disorders and Skin reactions to environmental agents. It does not aim to deal with imported or 'tropical' skin diseases. Dermatologists in training and those who are interested but not specially trained in dermatology will find this supplement of tremendous interest; it is packed with information and achieves the dual purpose of summarizing the current state of knowledge about most of the conditions which are important in American dermatology, while at the same time clearly indicating what remains to be done in the field of research.

[There is a note of particular interest to leprologists on page 475, in a section dealing with the development of drugs of limited commercial value:

'3. Dapsone: It has been known for many years that the drug, DDS, or diaminodiphenylsulfone (Dapsone), developed originally for the treatment of leprosy, is also effective for the treatment of dermatitis herpetiformis and several other rare, disabling and chronic skin diseases. DDS has been shown recently to have anti-inflammatory properties, particularly against the mediator bradykinin, which may account for some of its therapeutic activity. Because there are almost no other anti-inflammatory drugs that have distinctive anti-bradykinin effects, it seems inexcusable that DDS should be denied. In the course of a large screening effort to find better antimalarial drugs, the United States Army found that a derivative of DDS known as diformyl dapsone was much more effective than the dapsone itself. To our knowledge, there has been no attempt to investigate this drug further either for several skin conditions for which dapsone (DDS) is now used, or for the treatment of leprosy, which still afflicts tens of millions of people around the world.']

THE XVI INTERNATIONAL CONGRESS OF DERMATOLOGY, TOKYO, JAPAN, 1982

The XVI International Congress of Dermatology will be held in Tokyo, Japan, 23 to 28 May 1982. The Congress includes a scientific programme (special

lectures, case presentations, advances in dermatology, symposia, courses, workshops, informal discussion groups, free communications, poster communications, Japanese Dermatological Association seminars, and a scientific exhibition) and social events (performance of traditional Japanese Kabuki drama, a concert with a world-famous conductor, a short suburban sightseeing tour, and programmes for accompanying persons). The Congress site is the Hotel New Otani, Tokyo's prestige hotel which has been the site of many international congresses. English, French, Spanish, German and Japanese may be used in the Congress, and simultaneous interpretation will be provided during the main educational sessions.

The First Circular including detailed information regarding registration, hotel accommodations and group travel is now available on request to: Prof. Makoto Seiji, MD, Secretary General, The XVI International Congress of Dermatology, CPO Box 1560, Tokyo 100–91, Japan.

All interested persons are cordially invited to participate in the Congress.

COURSES OF INTEREST TO SCIENTIFIC AND TECHNICAL STAFF EMPLOYED IN THE NATIONAL HEALTH SERVICE (UK) 1978/1979

This is a 313-page book prepared by the Chief Scientific Officer's Unit, MED SM4, The Department of Health and Social Security, Alexander Fleming House, Elephant and Castle, London SE1. It reveals that an astonishing number of courses are available in different parts of the UK, and these include various aspects of bacteriology, biochemistry, immunology, immunobiology, medical microbiology, neurological sciences, pharmacological biochemistry, statistics, etc. Over 70 Master of Science (M.Sc.) and post-graduate diploma courses are listed in the introductory pages. The book is available free on application to the above address.

LA LEPRE CHEZ L'ENFANT

French translation of 'Leprosy in Childhood'; transparency teaching set with text by TALC, Institute of Child Health, 30 Guilford Street, London WC1N 1EH

Thanks to a great deal of painstaking work by Michel and Thérèse Thuriaux-Jacques, a complete French translation of this script is now available. Single copies may be obtained from the Editor of *Leprosy Review* in Oxford. This translation applies to Lp, not to the set on classification, LpCn. The actual sets and English scripts should be obtained from TALC in London, as above.

PICTORIAL AIDS FOR MEDICAL TEACHING: FROM THE MAGAZINE OF WHO, OCTOBER, 1979

Colour microfiche, a cost-effective system for disseminating teaching aids, will have a part to play in a special 'illustration bank' on tropical parasitology under WHO's health learning materials programme. The material is being made available in both slide and microfiche form, with exaplanatory texts.

A microfiche of 84 frames can be produced for around $100, and copies from this master set may be obtained for less than $1 each. The same material in slide form would cost about $35.00 per set.

The first set in the tropical parasitology programme is on schistosomiasis, and may be purchased from the Royal Tropical Institute, Department of Tropical Hygiene, 63 Mauriskade, Amsterdam-Oost, Netherlands. Other sets will be devoted to leprosy, malaria, leishmaniasis, trypanosomiasis, geohelminth infections, filariasis, amoe biasis, other helminth infections and other protozoal infections.

This series is the initial effort in a continuing programme to develop an international slide/microfiche bank on medical and health related subjects.

Several other institutions, particularly in the USA, are producing teaching programmes in this form. The American College of Physicians, Philadelphia, has developed self-instructional units for the continuing education of physicians, each comprising audio cassette, self-assessment test, and colour microfiche.

The University of Washington, Seattle, has also produced similar material in colour microfiche and can arrange to produce it for other organizations under contract.

Further information concerning colour microfiche systems can be obtained from Educational Communication Systems, Division of Health Manpower Development, WHO, Geneva.

PORTABLE SLIDE PROJECTOR, WEIGHING LESS THAN 5 Kg

SEMAT are the UK agents for a Kindermann AV 100 projector which, although not cheap, may be worth consideration by those who travel over large areas and are involved in teaching. The slide projection is fully automatic and shows up on a built-in 18 x 18 cm back projection screen, but it can also be used on a conventional wall screen by simply removing the carrying case lid. There is a continuous cooling fan for slides, even if they jam due to a bad mount. The case is robust and the whole unit weighs less than 5 kg. Apply to SEMAT (UK) 89, Lakeside Road, London N13 4PS.

SCHISTO UPDATE, OCTOBER–DECEMBER 1979

Published quarterly in cooperation with the National Library of Medicine, Bethesda, Maryland, through the use of MEDLARS (Medical Literature Analysis and Retrieval System); lists articles on schistosomiasis that have appeared in approximately 2,300 journals.

This publication is comparable to the *Excerpta Medica* system for leprosy (and many other diseases). The extraordinary range and depth of subject matter relating to schistosomiasis alone is a reminder of the fact (taken from the introductory pages of this October–December issue) that 'Parasitic protozoa and helminths have enormous potential utility as models for the study of regulation of the immune response, the alteration of cell membranes, and genetic control of the induction of new antigens'. Experimental systems currently under study include '. . . the antibody-dependent eosinophil killing of schistosomula, the actions of cytotoxic T cells, and the production of monoclonal antibodies using the lymphocyte hybridoma technique.'

Update is issued free of charge to all who request it; from The Edna McConnell Clark Foundation, 250 Park Avenue, New York, New York, 10017, USA

Lepr Rev (1980) **51**, 195–198

Letter to the Editor

In vitro stimulation of neutrophil motility in lepromatous leprosy

Sir,

It has been previously reported that ascorbate,[1, 2] levamisole,[3, 4] metoprolol,[5] propranolol[6, 7] and sotalol[5] can promote increased neutrophil migration *in vitro* and *in vivo*[2, 8, 3] in normal individuals and in individuals with abnormal leucotaxis. We have recently investigated the effects of these agents at concentrations which have been reported to stimulate leucocyte motility on the chemotactic responsiveness of neutrophils from patients with lepromatous leprosy. Blood neutrophils from these patients have markedly depressed neutrophil chemotaxis.[9] The abnormality is due to the presence of high levels of inactivators of chemotactic factors in the patients serum[10] and to the presence of cell-directed serum inhibitors of motility[11] and to acquired neutrophil intrinsic defects of locomotion.[11]

Twelve new untreated admissions which included six borderline (BL), two sub-polar (LI) and four lepromatous (LL) patients were investigated. The classification was based on the clinical and histopathological criteria of Ridley and Jopling.[12] All patients showed negative skin tests to lepromin. Heparinized venous blood was processed as previously described[7] and neutrophils resuspended to a concentration of 5×10^6/ml (in the presence or absence of the test agents) in Hank's balanced salt solution. The leucoattractant used was endotoxin activated autologous serum.[7] Neutrophil motility was assessed in a modified Boyden chamber using 5 μm pore size Millipore filters and a 3 hr incubation period.[7] Results are expressed as neutrophils per microscope high power field.

In a second series of experiments the ability of the same agents to inhibit the inhibition of migration of normal neutrophils in the presence of sera from the leprosy patients was assessed. Results of both series of experiments are shown in Table 1.

References

[1] Goetzl EJ, Wasserman SI, Gigli I *et al.* *J Clin Invest*, 1974, **53**, 818.
[2] Anderson R, Theron A. *S Afr med J*, 1979, **56**, 429.

Table 1. The effects of calcium and sodium ascorbate; levamisole, metoprolol and sotalol on (a) the chemotaxis of neutrophils from patients with lepromatous leprosy, and (b) the inhibition of chemotaxis of neutrophils from normal individuals in the presence of serum from patients with lepromatous leprosy

	Control (no drug)	1×10^{-2} M Calcium ascorbate	1×10^{-1} M Sodium ascorbate	1×10^{-3} M Levamisole	2.5×10^{-3} M Metoprolol	1×10^{-4} M Propranolol	2.5×10^{-3} M Sotalol
(a)	35 ± 15*	198 ± 85	232 ± 60	192 ± 70	158 ± 64	173 ± 53	162 ± 49
(b)	63 ± 11 (153 ± 21)†	192 ± 43	187 ± 37	191 ± 39	182 ± 42	192 ± 36	167 ± 31

*Results as cells/high power field as mean and standard error.

†Corresponding value for normal neutrophils incubated with 5% autologous serum.

The above results indicate that calcium and sodium ascorbate, levamisole, metoprolol, propranolol and sotalol can stimulate the chemotactic responsiveness of neutrophils from patients with lepromatous leprosy and eliminate the inhibitory effect of sera from patients with lepromatous leprosy on the motility of normal neutrophils. They may therefore be useful in the *in vivo* restoration of leucotaxis in these patients

[3] Anderson R, Glover A, Koornhof HJ *et al. J Immunol,* 1976, **117**, 428.
[4] Wright DG, Kirkpatrick CH, Gallin JI, *J Clin Invest,* 1977, **59**, 941.
[5] Anderson R. *S Afr med J,* 1979, **56**, 165.
[6] Anderson R, Van Rensburg AJ, *S Afr med J,* 1978; **53**, 694.
[7] Anderson R, Van Rensburg AJ, *Immunology,* 1979, **37**, 18.
[8] Anderson R, Oosthuizen R, Theron A *et al. Clin Exp Immunol,* 1979, **35**, 478.
[9] Bullock WE, Ho MF, Chen MJ, *J Reticuloendothel Soc,* 1974, **16**, 259.
[10] Ward PA, Goralnick S, Bullock WE, *J Lab Clin Med,* 1976, **87**, 1025.
[11] Sher R, Anderson R, Glover A *et al. Infec Immun,* 1978, **21**, 959.
[12] Ridley DS, Jopling WH. *Int J Lepr,* 1966, **34**, 255.

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We apologise most sincerely to Dr Felton Ross for mistakes in the printing of his letter on pages 92 and 93 of Leprosy Review, **51**, Number 1, 1980. It should correctly read as follows:–

Does clofazimine have any value in the management of reversal reation?

Sir,
With reference to the article on clofazimine in *Leprosy Review* **50**, 1979, 134–44, I would like to make the following comments:

Two papers (references 1 and 2 below) are frequently quoted in support of the contention that clofazimine is effective in the management of reversal reactions, but neither paper really makes the case.

In his paper Pfaltzgraff[1] states: 'All patients were given steroids for rapid relief of neuritic signs and symptoms.' In my view he makes a good case for the effectiveness of steroids in reversal reactions, but is less convincing regarding the effectiveness of clofazimine.

In her paper Schulz[2] writes: 'In our patients neuritis was adequately controlled after an average of $3\frac{1}{2}$ months of treatment with clofazimine.' I submit that average time lapse of $3\frac{1}{2}$ months before the control of neuritis is in reality evidence of the ineffectiveness of clofazimine in these cases.

Both Pfalzgraff and Schulz deserve thanks and congratulations for having

tackled a problem most of us have evaded, but surely it is time to settle the issue one way or the other. At least we should stop recommending clofazimine for the management of reversal reaction until more definite evidence is available.

Barnetson, *et al.*[3] have done leprosy patients a great service by exploding the myth of dapsone as a causative agent in reversal reactions by a controlled clinical trial. It is my belief that the alleged effectiveness of clofazimine in reversal reactions is also a myth. Have any of your esteemed readers evidence to the contrary?

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References

1 Pfaltzgraff RE. The control of neuritis in leprosy with clofazimine. *Int J Lepr,* 1972, **40,** 392.

2 Schulz EJ. Forty-four months experience in the treatment of leprosy with clofazimine. *Lepr Rev,* 1972, **42,** 178.

3 Barnetson R Stc, Pearson JMH, Rees RJW. Evidence for prevention of borderline leprosy reactions by dapsone. *Lancet,* 1976, **11,** 1171.

Editorial Note

Due to the unusual number of pages used in Number 1, (110 instead of 80), we regret that it is not possible to include *Book Reviews + Abstracts* in this Number; they will be carried forward to Number 3.

Some Northern States of the Federal Republic of

NIGERIA

have vacancies for

MEDICAL OFFICERS LEPROSY

The infrastructure of the leprosy services—in what used to be the Northern Region—established in the fifties (C. M. Ross) and consolidated in the sixties (D. L. Leiker) is still existing. Presently the general health services are in the process of being peripheralized further. Official policy is towards gradual integration. Leprosy services need strengthening and updating.
Main tasks for medical officers are:
Medical and surgical treatment of patients with complications referred to the leprosy hospitals.
In-service training of various categories of auxiliary and paramedical personnel.
Teaching where requested.
Supporting and strengthening the existing leprosy control services in (hundreds of) rural clinics.

Urgent vacancies exist in:

Babbar Ruga Leprosy Hospital, near Kaduna State

Babbar Ruga is a modest Leprosy Hospital, of approx. 80 beds, at 6 kilometres from Katsina (which has a fully staffed referral hospital with about 30 doctors). Emphasis is on field work: training and supervision of staff in field clinics. Population 4·5 million. Patients on register 23,000, many of them ready for release from control. Estimated prevalence of leprosy between 4 and 6 per thousand.

Gongola State Leprosy Hospital at Garkida in Gongola State

The State Leprosy Hospital at Garkida is widely known in the area for its outstanding surgical and physical rehabilitation services and its long-standing tradition of good leprosy teaching.

The present medical officer in charge, Dr Roy E. Pfaltzgraff (co-author with Bryceson of *Leprosy*, 2nd Edition, 1979), requires further support in order to provide adequate medical care, and also to cope with the training needs for further development of the Leprosy Control Service staff, who care for more than 18,000 leprosy patients. Teaching, training and health education are essential elements in the programme.

Gongola has an interesting experiment with rural basic health services with a remarkable participation of the community at village level. (See for this: Contact 41. Oct. 1977: Bulletin of the Christian Medical Commission of WCC, Geneva). It is vital to integrate leprosy care into this service at an early stage.

Leprosy Control and Training Centre near Zaria, Kaduna State

The LCTC of Zaria, not far from the Ahmadu Bello University, is earmarked as the main training centre for leprosy work in Northern Nigeria. The hospital itself needs improvement both in facilities equipment and staffing, for which the first phases of a masterplan are being implemented.

Attached to the LCTC was recently a Leprosy Research Unit. This unit is just starting (1979/80) with a modest programme of applied research aiming at assessment of dapsone resistance, optimalization of chemotherapy regimens and improvement of patient compliance.

Terms of service and living conditions for all mentioned posts are relatively fair to good. More information can be obtained from:

Netherlands Leprosy Relief Association (NSL), c/o Royal Tropical Institute, Mauritskade 63, 1092 AD AMSTERDAM, The Netherlands.

®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].

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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)