Lepr Rev (1984) **55,** 89–104

Occasional Review—HLA and Leprosy: a Re-evaluation

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Introduction

The discovery in experimental animals of immune response genes (Ir-genes) located in the Major Histocompatibility Complex (MHC), provided an impetus for exploring HLA—the human MHC—encoded genetic control of the immune response in man. In this area particular attention was paid to leprosy on the supposition that genetic factors were involved in this disease, in the variable immune status of the patients, and in the specific immune defect in leprosy-affected patients. In many studies on the distribution of HLA-phenotypes among groups of patients and controls and among the members of multi-case leprosy families a role for HLA-encoded factors in the susceptibility to leprosy was shown, but entirely and quite unexpectedly, to tuberculoid leprosy and not lepromatous leprosy. These studies were reviewed previously.[1] However, more recent studies gave convincing support to a more general role for HLA in determining the type of the disease to develop following infection. At the present stage it seems justified to state that the susceptibility to both polar tuberculoid (TT) and lepromatous (BL/LL) leprosy is controlled, at least partly, by HLA-linked genes and that these genes do not influence susceptibility to leprosy *per se*, but rather determine the type of disease to develop, most probably by controlling the leprosy-specific immune response.

Recent findings based on population—and family studies as well as *in vitro* experiments, to investigate the role of HLA in leprosy—will be discussed in the present review.

The biological significance of the HLA-system

The HLA-system is recognized as a major immunogenetic and histocompatibility system, coding for a large multi-allelic family of cell-membrane molecules and glycoproteins, present on the cell membrane of virtually all nucleated cells. Since

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the HLA-molecules were originally detected on leucocytes, the initials 'HL' (Human Leucocyte) were given. However, these initials may equally well be considered to indicate Histocompatibility Locus. 'A' is commonly supposed to stand for Antigen, although originally it indicated that it was the first system of its kind to be recognized in man. For a description of the genetic aspects of the HLA-system see previous review papers.[1–3] A unique feature of the HLA-system, undoubtedly closely related to its biological significance, is its extraordinary polymorphism. How such polymorphism could have been maintained during evolution began to be appreciated from the findings that the products of the HLA-system were central in determining the immune response. At present it is well known that T-lymphocytes, in their function as regulator and as effector cells in the immune response, recognize foreign antigens in association with products of the HLA-system. This phenomenon, called HLA-restriction has been described extensively.[4] With respect to this phenomenon it has been shown that a foreign antigen may be recognized in association with certain HLA-antigens more efficiently than in association with others. Therefore, the range of antigens present on the variety of offending pathogens recognized by the immune system of an individual host, may be determined, at least partly, by the complexity of the host HLA-system. The ensuing advantage of the heterozygous individual may be one of the driving forces in maintaining the polymorphism of the system.[5]

As a corollary of the biological significance of the system, the presence of individuals with varying immunological potential to a given antigenic challenge was to be anticipated. It is not surprising, therefore, that the HLA-system was found to influence the degree of susceptibility or resistance to diseases implicating the immune system.

HLA and infectious disease

Although the HLA-system is assumed to be critical to the way the body deals with infectious agents, the number of studies on HLA and infectious diseases has remained small as compared to the number of studies addressing themselves to non-infectious diseases. A plausible explanation for this could be that infectious diseases have nowadays become a public health problem of primary importance in the tropics and third world countries, whereas the HLA-laboratories have been concentrated, so far, in the developed countries. Nevertheless, in the field of HLA and infectious disease, some progress has been made and evidence for a role of HLA-determinants in infectious diseases is accumulating.[6]

A considerable number of studies, however, failed in tracing down HLA-encoded factors as risk factors for infection.[7] This could be interpreted to indicate that most deleterious susceptibility factors have been lost during evolution and that only factors imposing subtle differences in resistance have remained in existence, especially with respect to diseases with high-case fatality rates early in life. Another factor contributing to the failure of studies designed to detect

HLA-encoded control of infectious disease could be 'disease heterogeneity'. Bearing in mind the potential role of the HLA-system in guiding the immune response both in a quantitative and in a qualitative way, the influence of HLA could become reflected in the height or the type of immune response generated during infection. For this reason the patient groups under study should be carefully screened for heterogeneity of immunological aspects during infection or for heterogeneity of eventual immuno-(patho-)logical consequences of the disease. Additional confounding effects may result from environmental factors. Differences in individual level of exposure to an infectious agent obviously constitutes one of the environmental factors which contributes to the differential occurrence of the disease among the population and may well obscure a possible modest effect of HLA on disease resistance. Finally, successful detection of HLA-encoded risk factors could have been hampered by the incomplete recognition of the relevant products of the HLA-system, being especially pertinent to the HLA-D/DR region, the region within the HLA-system harbouring the majority of genes relevant to the regulation of the immune response.

Leprosy: 'a model disease'

The etiological agent in leprosy, *Mycobacterium leprae*, is in itself virtually non-toxic. Clinical symptoms of the disease, such as nerve damage, depend largely upon immune reactions directed against the microorganism or antigenic substances liberated from it. Acknowledging the unique opportunities in leprosy to study the immune mechanisms resulting from host–parasite interactions, it was stated by Harboe & Closs that leprosy is developing as a 'model disease, which provides essential information on the importance of immune reactions in several chronic infectious diseases'.[8]

One of the most intriguing features of leprosy is the obvious inter-individual variety in symptomatology to develop after infection. The majority of individuals are fully resistant or develop an effective immune response upon exposure to *M. leprae*, protecting them from developing disease. A minority, on the contrary, are lacking resistance or effective immune reactivity and will develop the disease after becoming infected. Apparently, depending on the degree of immune response that is subsequently generated, either 'low resistant' or 'high resistant' forms of the disease will develop. Following the leprosy spectrum,[9] starting with polar tuberculoid leprosy (TT) and ending up with polar lepromatous leprosy (LL), a continuous decrease of activity of cell-mediated immunity is found.[10] By now it has become widely accepted that host-dependent variation in immune status is responsible for the diversity of the clinical appearance of leprosy, although the host factors determining the host-immune status towards *M. leprae* still remain to be elucidated. However, mainly as a result of recently obtained information on HLA and leprosy, a possible role of genetic factors in this regard has presently

received renewed interest. Crucial in studying how host factors determine the host-immune status could be the proper delineation of the nature of the immune defect in leprosy. In this respect much attention has been paid to the anergic state of lepromatous leprosy. Besides some degree of a generalized depression of the cell-mediated immunity in this type of leprosy, the deficiency of cell-mediated immunity specific for *M. leprae* is more pronounced and seems to be irreversible following successful treatment of the disease.[11, 12] The pre-existence of the defect prior to the development of clinical disease or the presence of the defect in healthy individuals is controversial.[13]

The nature of the immune defect underlying the specific anergy in lepromatous leprosy has been investigated by various approaches. Evidence was collected in favour of roughly three different mechanisms, which show remarkable similarities with the mechanisms proposed to be responsible for MHC-linked Ir gene defects. Firstly, lepromatous leprosy patients have been shown to lack circulating T-lymphocytes capable of responding to *M. leprae* in the lymphocyte transformation test.[14, 15] Secondly, abnormal macrophage function with defective presentation of *M. leprae* antigens to the immune system in lepromatous leprosy has been reported.[16] Thirdly, evidence for suppression of the immune response by suppressor T-cells in lepromatous leprosy was obtained.[17] The recent observation that the leprosy specific non-responsiveness *in vitro* appeared to be reversible upon the addition of interleukin 2, provides additional support for the third mechanism.[18] Nevertheless, although the third mechanism seems the most plausible and attractive, in essence the question of the nature of the immune defect in lepromatous leprosy is still open. The immunological defect leading to the development of (polar) tuberculoid leprosy has remained even more obscure. Although in some experiments the presence of suppressor T-cells was shown to be a feature of tuberculoid leprosy and not of lepromatous leprosy,[19] so far no specific immune defect has been found in relation to tuberculoid leprosy.

Genetics of leprosy

The first studies concerning heredity and leprosy date back to the 1840s, when Danielssen & Boeck[20] concluded that there was a definite familial spread of leprosy. However, since the discovery of *M. leprae* as the causative organism in 1874 by Hansen, the hereditary aspects of leprosy were long neglected. Although Aycock & McKinley[21] speculated on a role of genetic factors in the resistance to leprosy among family-members, a proper reassessment of genetics and leprosy started with Spicket[22] who attributed both the relative restriction of leprosy to certain ethnic groups and the differential occurrence of leprosy among families to genetic factors. Furthermore, he considered the type of leprosy to be influenced by genetic factors in a multifactorial way. Additional data favouring genetic aspects of the type of leprosy within families were collected by Beiguelman.[23] He

observed a relatively high concordance of leprosy type among sib-pairs and stated that children of lepromatous parents tended to develop lepromatous leprosy. He also studied lepromin skin-test responses within families and among twins. Despite the rather nebulous outcome of these studies, they were interpreted to show genetic aspects of the predisposition to leprosy. A more thorough twin-study was carried out by Chakravartti & Vogel.[24] Although the outcome of this study may to some extent have been confounded by ascertainment bias, a number of interesting observations were made. Among 62 monozygotic twin-pairs 37 were found to be concordant for leprosy, as compared to eight being concordant for leprosy among 40 dizygotic twin-pairs. Among pairs of which at least one twin had lepromatous leprosy, the concordance for lepromatous leprosy was 70% for monozygotic pairs and only 20% for dizygotic pairs. From these twin data it was concluded that the risk of developing leprosy depends both on genetic and on environmental factors and that the type of leprosy is strongly influenced by genetic factors. More recently, on the basis of a complex segregation analysis in families, Smith[25] showed genetic control of susceptibility to lepromatous leprosy. An argument was put forth in favour of a multifactorial model of genetic control with a heretability of about 80%. Additional and similar pedigree data on leprosy, collected by Serjeantson *et al.*,[26] were also demonstrated to fit a multifactorial model.

In conclusion, the number of studies indicating genetic control in leprosy has been substantial, but the data generated have remained frequently multi-interpretable and subject to dispute.[27]

Studies of HLA and tuberculoid leprosy

Since the time the HLA-system was supposed to contain genes playing a role in regulating the immune response, various studies were carried out analysing HLA-A and -B antigen distributions among leprosy patients and healthy controls in different populations.[28–43] Due to differences in or absence of a proper classification of the patients and doubtful appropriateness of the selected control groups in some instances, it is difficult to make proper comparisons. Nevertheless, the frequencies of two HLA-specificities have been observed repeatedly to differ between patients and controls. HLA-A9 was observed to be decreased among tuberculoid leprosy patients in Thailand,[37, 39, 41] among Chinese tuberculoid leprosy patients from Singapore[42] and among non-lepromatous leprosy-affected patients in India.[33] An increase of HLA-A9 has been reported for lepromatous leprosy patients in Japan.[38] It has been found that HLA-B17 has increased among tuberculoid leprosy patients in Thailand[37, 39, 41] and in Singapore (Chinese).[42] Additional associations, remaining significant after correction for the number of comparisons made and not being disputed by subsequent studies, have been reported for HLA-Bw21 with tuberculoid leprosy in Ethiopia[28] and for HLA-B14 with lepromatous leprosy in Spain.[30]

Reviewing all data concerning HLA-A and -B associations with leprosy, the conclusion seems inevitable that the evidence in favour of a role for HLA-A and -B determinants in leprosy is not impressive. A number of studies provided no evidence at all, whereas the associations reported are mostly weak and confined to the population studied. The explanation for this situation may be that the HLA-A and -B antigens are not directly responsible for the differential leprosy susceptibility, but that they do occur in some populations in linkage disequilibrium [44] with the hypothetical 'susceptibility genes' for leprosy.

The method of first choice to overcome difficulties imposed by population-dependent differences in linkage disequilibrium is the study of families. Moreover, family studies may even reveal HLA-linked control in the absence of associations at the population level. In three family studies, one carried out in Surinam[45] and two carried out in India,[46, 47] a segregation analysis has provided evidence in favour of recessive HLA-linked factors conferring susceptibility to polar tuberculoid leprosy. Data collected were insufficient to allow a proper assessment of HLA-linked control of other forms of leprosy. The result of a recently reported classical linkage analysis of the above-mentioned family data and some additional family data by the method of lod-scoring has not provided essential additional information regarding the previously reported[46, 47] recessive inheritance of HLA-linked susceptibility to tuberculoid leprosy.[48] In one of the above-mentioned family studies in India[46] HLA-DR2 was observed to be associated with tuberculoid leprosy. Although this finding was confirmed in a subsequent family study,[49] the frequency of DR2 among sporadic cases of tuberculoid leprosy in the same Indian area was shown not to be increased,[50] suggesting a genetic heterogeneity between familial and sporadic tuberculoid leprosy. However, independent studies in other populations did show an association of HLA-DR2 with tuberculoid leprosy.[51–53] Also, in Japanese studies, DR2 was shown to be associated with lepromatous leprosy[52, 53] and in a different Japanese study, restricted to tuberculoid leprosy, the increase of DR2 among the patients was found to be secondary to an association with HLA-MT1, one of the more recently detected HLA-class II determinants.[54] In the other above-mentioned studies[52, 53] HLA-MT1 was also found to be increased among tuberculoid leprosy patients and to an even greater extent among patients with lepromatous leprosy. On the basis of the above data on HLA and leprosy, HLA-linked control of susceptibility to tuberculoid leprosy seems likely. Furthermore, the prediction based on functional grounds that more consistent associations would be detected with HLA-DR or additional class-II products, seems to be true.

Recent studies implicating a role of HLA in the susceptibility to lepromatous leprosy

One of the studies suggesting a role of HLA, not only in the susceptibility to tuberculoid leprosy, but also to lepromatous leprosy has already been

mentioned.[1] Among a group of mixed Caucasoid–Negroid patients originating from Surinam not only was a higher frequency of DR3 observed among TT leprosy patients as compared to healthy controls, but also DR3 was found to be almost absent among lepromatous (BL and LL) patients.[55] This indicated that in this population HLA-DR3 or an HLA-DR3 associated factor confers resistance to lepromatous leprosy. The markedly decreased frequency of DR3 among lepromatous patients from this population, which was not observed for DR2 among the lepromatous patients from studies showing an association between TT leprosy and DR2, indicates that the DR3-associated control of leprosy type is different from the previously discussed one associated with DR2. Therefore, the observation that susceptibility to polar tuberculoid leprosy is associated with DR2 in India and with DR3 in Surinam, is most likely explained by the existence of different genes, which may predispose to tuberculoid leprosy. Alternatively this discrepancy may be explained by the action of other genes not linked to HLA present in the population. In both situations the relevant HLA-linked gene(s) may be either DR itself, or a separate gene(s) in linkage disequilibrium with DR2 or DR3, depending on the population examined. In two of the previously described population studies data on HLA-DR3 both show an increased (but not significant) frequency of DR3 among tuberculoid leprosy patients.[50, 51] In the Japanese population HLA-DR3 does not occur.[52, 54]

More convincing data, suggesting a role of HLA in lepromatous leprosy, were obtained from recent HLA-haplotype segregation data of multi-case lepromatous leprosy families from Venezuela.[56] Although hardly any information based on families with lepromatous leprosy was obtained previously, there seemed to be a general agreement that any non-random inheritance of HLA-haplotypes in leprosy families would be confined to tuberculoid offspring.[1, 57, 48] The family data from Venezuela, however, attempted to break with this ill-based dogma. The segregation pattern was found to be highly non-random, especially for haplotypes derived from lepromatous (BL and LL) leprosy-affected parents. In the same families from Venezuela the non-random segregation of HLA-haplotypes in polar tuberculoid leprosy patients was confirmed, indicating again recessive HLA-linked susceptibility to tuberculoid leprosy. Some of these segregation data are shown in Table 1. The data for lepromatous (LL/BL) leprosy-affected siblings indicate convincingly the presence of HLA-linked genes predisposing to lepromatous leprosy. In particular, the finding that the HLA-haplotype segregation for parents affected with lepromatous leprosy was observed to occur non-randomly, suggests a dominant pattern of inheritance of the predisposition to lepromatous leprosy. A similar non-random distribution of parental HLA-haplotypes among lepromatous leprosy affected sibs was observed in a recent family study carried out in China.[58] However, since in the latter study hardly any families were available with parents suffering from lepromatous leprosy no support for the dominant character of this HLA-linked control of lepromatous

Table 1. Parental HLA-haplotype segregation in multi-case leprosy families from Venezuela

Siblings	Parents	Observed ΣD*	Expected Σd*	$\Sigma\sigma^2 d$*	χ^2	p†
BL/LL leprosy	Healthy	28	22	20		n.s.
	LL leprosy	21	12·5	10·25	6·24	0·006
		49	34·5	30·25	6·48	0·005
TT leprosy	Healthy	10	7	5·5		n.s.
	LL leprosy	13	8·5	6·25	3·24	0·04
		23	15·5	11·75	4·17	0·02

*D = Observed difference between the number of affected siblings with one and those with the other haplotype.
d = Expected difference for random segregation.
$\Sigma D > \Sigma d$ = An excess of identical HLA-haplotypes.
$\sigma^2 d$ = Variance of d. For method of analysis see ref. 45.
† p-value is divided by 2 (one-sided significance test).
n.s. not significant.

leprosy was obtained. The combined HLA-segregation data from more than 120 families collected so far[45, 47, 49, 56, 58] are presented in Table 2.

In view of the increasing evidence of suppressor T-cells in lepromatous leprosy[59, 18] the HLA-linked control of lepromatous leprosy is likely to be due to an Is gene. The existence of such, presumably, leprosy-specific immune suppression (Is) genes should have far-reaching practical and theoretical

Table 2. Children suffering from TT or BL/LL leprosy share HLA-haplotypes more frequently than expected*

Children	Observed ΣD	Expected Σd	χ^2	p-value†
1. TT leprosy‡	188	139·6	19·36	5×10^{-6}
2. BL/LL leprosy	89	64·5	10·06	0·0008
3. Healthy§	128	125·8	0·03	n.s.

* For method of analysis see ref. 45.
† p-value divided by 2 (one-sided significance test).
‡ Offspring of TT parents not included.
§ Healthy sibs older than youngest patient only.
n.s. not significant.

implications for prevention or therapy of the disease and for our understanding of the immune defect in lepromatous leprosy. Besides this, it could indicate that the action of Is genes is an essential aspect of the mechanisms controlling the immune response in man.

Susceptibility to leprosy *per se* not controlled by HLA-linked genes

As already shown in Table 2 for the combined family data, the segregation of HLA-haplotypes among healthy siblings in multi-case leprosy families was observed to occur randomly in the studies carried out so far. This repeatedly made observation argues against the existence of HLA-linked genes conferring susceptibility to leprosy *per se*. In the presence of such genes, a preferential segregation of parental haplotypes lacking these susceptibility genes would have been observed among the healthy sibs. Furthermore, if genes conferring susceptibility to leprosy *per se* were linked to HLA, one would expect those HLA haplotypes shared between all leprosy patients in a given sibship ('leprosy-haplotypes') to occur less frequently among the healthy siblings of that sibship. That this was not the case is shown in Table 3 for data obtained in India, Venezuela and China.

Therefore, whereas the type of leprosy to develop in individuals who are susceptible to leprosy seems to be determined, at least partly, by HLA-linked genes, the susceptibility to leprosy *per se* seems not. Most probably, the susceptibility to leprosy *per se* is influenced both by environmental factors and non-HLA encoded genetic factors. The latter supposition is mainly inferred from

Table 3. Analysis of the presence among healthy siblings of HLA-haplotypes which are shared among all leprosy patients in the sibship ('leprosy-haplotypes')

	Number of 'leprosy-haplotypes'		
Healthy siblings*	obs.	exp.‡	*p*†
India[47]	40	40·5	n.s.
Venezuela[56]	22	24	n.s.
China[58]	19	16	n.s.
	—— +	—— +	
	81	80·5	n.s.

* Healthy sibs older than youngest patient only.

† Method of analysis described previously see ref. 58.

‡ Expectation on the basis of random haplotype distribution.

n.s. not significant.

experimental mouse models, which showed for various intracellular micro-organisms that the innate resistance towards them is controlled by a single gene not linked to the H-2 system (the murine MHC).[60–62] The modifying influence of H-2-linked genes only in the acquired phase of immunity has also been shown in a number of these experimental models.[63–65] At variance with these findings and, therefore, of special interest could be the recent finding of control of bacterial multiplication by H-2-linked genes in *M. lepraemurium* infection.[66]

HLA-associated markers for leprosy

The data collected so far with respect to HLA-associated markers for leprosy (types) are not clearcut. Nevertheless, from the data collected, one might infer that such markers do exist and are coded for mainly in the HLA-DR region. The evidence in favour of DR2, DR3 and MT1 being such markers has already been mentioned. Recent confirmative evidence for a role of DR3 and MT1 was obtained in the families from Venezuela (Table 4). Whereas MT1 was found to be inherited at preference by lepromatous leprosy affected children, DR3 was preferentially not inherited. In a limited population study of lepromatous leprosy in Venezuela, MT1 was also shown to be associated with this type of the disease.[67] In spite of the seeming consistency in the data implicating a role of particular class II determinants (DR, MT) in the predisposition to leprosy types, the associations found so far are too weak to be of any practical use. In the hope of obtaining more useful markers for the predisposition to particular leprosy types, further association studies will have to be carried out in various populations on well-classified patients, both familial and sporadic. With the better recognition of the non-DR class II determinants and with the help of more recently developed tools such as monoclonal antibodies recognizing distinct epitopes on class II

Table 4. Inheritance of HLA-DR3 and -MT1 from, respectively, DR3- and MT1- heterozygous parents in relation to leprosy status

Leprosy status children	DR3 inherited	DR3 not inherited	p*	MT1 inherited	MT1 not inherited	p*
BL/LL leprosy	2	9	0·03	30	17	0·04
TT leprosy	9	4	n.s.†	6	6	n.s.
healthy‡	12	10	n.s.	24	26	n.s.

* Pr from binomial distribution with $p = 50$.

† Significant difference between BL/LL and TT ($p = 0{\cdot}02$).

‡ Only healthy children, being older than youngest affected child, are included in the analysis.

n.s. not significant.

molecules and cDNA probes recognizing DNA fragments in the genome coding for HLA-Class II molecules and flanking sequencies, it is expected that the relevant genes or gene products will be recognized in a more reliable way.

HLA-DR associated control of *M. leprae* specific immune response *in vitro*

Since the cellular immune response, as measured by the lymphocyte transformation test (LTT) in sibs being HLA-identical with their TT leprosy affected sibs, did not differ from that in sibs being HLA-non-identical with their TT leprosy affected sibs, it was concluded that it would be impossible to study the expression of the HLA-linked genes predisposing to tuberculoid leprosy by a standard LTT.[68] Therefore, a more sophisticated test-system was applied to study specifically the role of HLA-DR molecules in the interaction between antigen-presenting cells (APCs) and T-cells in *M. leprae* specific proliferative responses.[69] For this purpose T-cells obtained from HLA-DR3 positive Surinam tuberculoid leprosy patients were studied for their proliferative responses against *M. leprae* antigens using monocytes obtained from various healthy individuals as APCs. In these experiments the HLA-DR restriction was shown for the first time, indicating a role of HLA-DR molecules in *M. leprae* specific proliferative responses, as was also indicated by the blocking effect of anti-DR antibodies in proliferative responses.[70] Furthermore, it was observed that the responses directed against the *M. leprae* derived antigenic cell-wall fraction, MLW-1,[71] obtained with DR3 homozygous monocytes as APCs were of a lower level than the responses obtained with DR-non3 homozygous monocytes (Figure 1). This, especially, indicated a poor capacity of DR3 to function as a restricting molecule in the immune response to leprosy-specific antigenic determinants. From the data

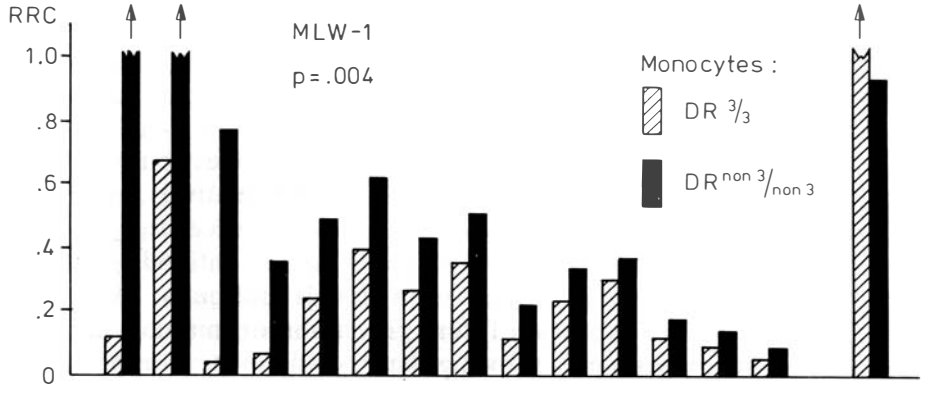

Figure 1. Proliferative responses of T-cells obtained from 15 HLA-DR3 heterozygous individual T-cell donors, co-cultured with either DR3 or DR-non3 homozygous allogeneic DR-compatible monocytes as antigen-presenting cells (APCs) for MLW-1 antigen. RRC denotes relative regression coefficient (slope) as calculated by an analysis of regression of response on MLW-1 dose.[69]

obtained it is concluded that T-cell recognition of leprosy-specific antigens in conjunction with HLA-DR3 is poor. However, in view of the immunological features of tuberculoid leprosy, such as specific responsiveness in the standard LTT and lepromin skin-tests, one would have expected DR3-restricted responsiveness to be high rather than low. Therefore, the exact nature of the cellular mechanisms underlying the observed *in vitro* phenomenon should be clarified to see whether the data obtained in this experimental system are at all comparable with data obtained by the standard LTT and lepromin skin-test, and to exclude the possibility that we are measuring an *in vitro* artefact. Nevertheless, a poor recognition of leprosy-specific antigens could be compatible with the suggestion made in relation to skin-test data reported previously,[72] namely that individuals carrying DR3 preferentially recognize mycobacterial 'common-antigens'. It is self-evident that any poor or aberrant recognition of certain leprosy-specific determinants may have crucial consequences for the specific immune response in the *in vivo* situation. Since the experimental data may represent an *in vitro* correlate for an *in vivo* defined HLA-association, the test-system could offer possibilities to study the differential capacity of particular HLA-DR molecules to function as restricting elements as a mechanism for the HLA-linked genetic control in leprosy.

Perspectives

The recent findings described in the present paper provide a number of starting points for further in-depth investigation. With respect to practical implications for leprosy control, but also with respect to the understanding of, presumably, some essentials of the genetic control of the immune response in man, the HLA-linked control of the susceptibility to lepromatous leprosy deserves special attention. For obvious reasons, attempts should be made to test the hypothesis of leprosy-specific Is genes. One approach could be to present leprosy antigens to T-cells from lepromatous leprosy patients by allogeneic antigen presenting cells which share only one haplotype or one DR specificity with the T-cell. In this way, responses restricted by the responder haplotype or molecules could be obtained circumventing the involvement of Is gene products. Alternatively, attempts may be made to block the Is gene products, as was shown successfully in non-responder mice for the LDH-B antigen,[73] with the use of antibodies, preferably monoclonal, recognizing distinct epitopes on class II molecules. That the latter approach could have an impact on future prevention or immuno-therapy was indicated by mouse experiments showing that the administration of antibodies directed against certain class II H-2 products could prevent or modulate immunopathological disease processes.[74, 75] Speculating along these lines one could think of adding antibodies directed against leprosy Is gene products, possibly MT1, as non-conventional 'adjuvants' to vaccines used for prevention or

immuno-therapy. By blocking the effect of the presumed leprosy-specific Is gene products, one might be able to convert specific non-responders into responders. A promising beneficial therapeutic effect of multiple inoculations with a mixture of *M. leprae* and BCG has been shown in some but not all BL and LL patients.[76] The addition of the proper blocking antibodies to such a 'vaccine' could thus be one of the possibilities to raise the effectiveness of this kind of immunotherapy. To improve our understanding of the HLA-associated control in leprosy, better tools for investigation are expected to become available, namely antigen-specific T-cell lines grown from leprosy patients (and healthy controls). These can be studied for HLA-class II restriction properties for leprosy antigens presented by selected allogeneic antigen presenting cells obtained from both healthy individuals and leprosy patients.

Acknowledgments

This report is in part supported by the Dutch Foundation for Medical Research (FUNGO) which is subsidized by the Dutch Organization for the Advancement of Pure Research (ZWO), the J A Cohen Institute for Radiopathology and Radiation Protection (IRS) and the Immunology of Leprosy (IMMLEP) component of the UNDP/World Bank/WHO special Programme for Research and Training in Tropical Diseases.

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Leprosy of the eye—a general outline

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Summary Ocular complications from leprosy (Hansen's disease) seriously threaten a patient's quality of life.

The eye (the anterior segment structures) may be infiltrated and damaged by the mycobacteria directly; may suffer damage from inflammation (Type II reaction), and be damaged as a result of changes in the extraocular structures. These are features of the disease at or near the lepromatous end of the spectrum.

In addition to direct damage, the eye in about 15–20% of patients irrespective of their disease type, is subject to abnormal exposure due to nerve damage. This may be motor (C.7) causing lagophthalmos, or sensory (terminal branches of ophthalmic division of C.5) causing corneal hypaesthesia. Secondary infection by other pathogens complicates the damage initiated by dryness and trauma.

The patient most at risk is the one with active, long-standing lepromatous disease. He/she will possibly have diminished pain sensitivity. Symptoms will be unreliable. Routine objective examination of such patients becomes mandatory. Fortunately, most of the significant pathology is visible with the help of relatively unsophisticated instruments. A useful examination may be done in 2 or 3 minutes once the routine has become established.

An outline of pathophysiology, diagnosis and management of the main features of ocular leprosy have been presented in this article. Its aim has been to help the physician or other health worker to assume responsibility for the primary eye care of their leprosy patients and thus reduce the possibility of blindness. Loss of sensation of the extremities is a serious handicap to any individual. Blindness superimposes an intolerable burden.

Introduction

Leprosy is a disease which causes disability by affecting hands, feet and eyes. The purpose of this paper is to give an overall perspective on the effects of leprosy on the eye in a logical outline form and to indicate in a broad outline form what can go wrong, how to recognize it and how to manage the problem. Further reading and consultations with ophthalmologists are highly recommended in order to get a working knowledge of leprosy of the eye.

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The eyes are involved in leprosy in four ways:

Abnormal exposure of the eyes secondary to involvement of the 5th and 7th cranial nerves.
2 Infiltration of the eyes and/or eyelids by the leprosy bacillus.
3 Inflammation of the eyes secondary to the infiltration by the leprosy bacillus.
4 Complications secondary to involvement of neighbouring structures: eyelids, lacrimal glands and the naso-lacrimal drainage system.

Note. Not all patients will have all of these problems. The patient most at risk is the long-standing lepromatous case.

Exposure

Exposure has dual etiology:
1 Sensory loss—5th nerve damage.
2 Motor loss—7th nerve damage.

The patient with sensory loss can blink, but does not as often as necessary or with full potential due to the lack of pain. The patient with motor loss wants to blink but cannot adequately. There can be varying combinations and degrees of damage to the two nerves. Tuberculoid, borderline and lepromatous cases can all be affected.

SENSORY LOSS (5TH NERVE DAMAGE) PATHOPHYSIOLOGY

Corneal and conjunctival anaesthesia. (It is actually a hypaesthesia, but the word anaesthesia is commonly used.) Injuries, dryness of the cornea, infections and inflammations are *ignored by the patient* due to a decreased sensation. Total anaesthesia is rare. But even partial anaesthesia (hypaesthesia) can seriously affect the prognosis.

Diagnosis

1 Observe the patient for an abnormality of spontaneous blinking.
2 Evaluate corneal sensation with a wisp of cotton.
3 Symptoms are not proportionate to the signs (due to anaesthesia).
4 Check the inferior aspect of cornea for the signs of dryness. Confirm this with fluorescein staining.

Management—See below with 7th nerve.

MOTOR LOSS (7TH NERVE DAMAGE)—PATHOPHYSIOLOGY

The orbicularis oculi muscles are paralysed to varying degrees when the

zygomatic branch of the 7th nerve is affected. Lagophthalmos, or the inability to close the eyes, results in:

1 Drying of the eyes; especially while sleeping.
2 Exposure of the eyes to more danger due to the loss of protective blinking when the eyes are threatened.
3 Increase in eye infections and irritation due to lack of normal eyelid and tear physiology.

Diagnosis

1 Instruct the patient to close the eyes first as in sleep and then with maximal effort. There is weakness of the orbicularis muscle and possible lagophthalmos.
2 In spite of severe symptoms of dryness (burning, irritation and tearing) the eye may look fairly normal.
3 Evaluate the cornea by fluorescein staining.

Management (sensory and motor loss)

1 Educate the patient as to the dangers of the condition. He should be taught self-examination by checking for redness of the eyes with a mirror and monitoring his own vision. A dry cornea may decrease visual acuity by 50% or more.
2 Periodic clinical examinations.
3 Blinking exercises to strengthen unparalysed muscle fibres.
4 Artificial tears, e.g. methylcellulose, polyvinyl alcohol or castor oil. The patient with sensory loss *must* use drops regularly even if symptom-free. The patient with sensation *will want to use* the drops to relieve discomfort.
5 Taping the eyes shut at night, if indicated. (Caution: be sure to learn the proper technique before doing this so as not to damage the cornea.)
6 Protective eyeshield, if indicated. This forms a moisture chamber and protects the eye from trauma as well. (Used X-ray film is a good source of material to make eye-shield cups.)
7 Tarsorrhaphy, if indicated. A simple procedure; especially indicated in anaesthetic eyes showing corneal damage. A temporary tarsorrhaphy effective for 2–3 weeks can be achieved by a simple horizontal mattress suture across the palpebral fissure.
8 Temporalis muscle tendon transfer. Requires a skilled surgeon and a *motivated patient* who will use it regularly. Patients with anaesthetic eyes will not use it properly.

Direct infection of the eye by *Mycobacterium leprae*

GENERAL INFORMATION

This affects patients at the lepromatous end of disease spectrum. It is a

blood-borne infection. The lesions are confined to the anterior segment structures of the eye (cooler tissues), i.e. the cornea, conjunctiva, episclera, sclera, iris and ciliary body. The lesions, or infiltrates, usually become visible 4 or more years after the onset of the disease. In the early phases of the disease this lepromatous infiltration of the eye causes little, if any inflammation. Symptoms are absent and the eyes are white; however, patients must be warned that the eyes, along with the skin and other organs, are likely to become inflamed later. With effective treatment the disease should eventually arrest. But if a relapse occurs, the new infiltrates will provoke serious and destructive inflammation. The patients most at risk are those with a history of 20 or more years of lepromatous disease.

CORNEA PATHOPHYSIOLOGY

By corneal microscopy, early lesions are seen in the corneal nerves and subepithelial layer. The infiltrates start superficially and peripherally in the upper temporal quadrant. As the disease advances into other quadrants and the pupillary area, new infiltrates may develop peripherally in the deeper layers of the cornea. The lesions start discretely, but later coalesce. At first they are avascular, but secondary pannus may follow.

Symptoms

None, unless the pupillary area is involved reducing visual acuity.

Signs

Haziness of the cornea mostly in the upper temporal quadrant. 'Pearls' may be seen resembling chalk dust.

Diagnosis

Penlight, magnifying loupe. A darkened room is an advantage. The patient looks down and the examiner retracts the upper eyelid and focuses on the upper temporal quadrant.

Management

Systemic anti-leprosy drugs. With the disease under control infiltrates slowly resolve. Residual scarring may persist but visual acuity should improve somewhat. If a vascular pannus has formed, prognosis for an improvement of vision is guarded. Warn the patient about future inflammation, how to recognize it and what to do. (See section on inflammation, below.)

IRIS

The earliest lesions are not visible until the tiny iris lepromata or 'pearls' form. They resemble chalky particles on the iris surface. They are first seen close to the pupillary margin. Larger, hypopigmented nodules are very occasionally seen in highly active, long-standing disease.

Symptoms

None.

Diagnosis

Penlight, darkened room, and focal oblique illumination. Large 'pearls' can be seen with a magnifying loupe, small ones require greater magnification (corneal microscope).

Management

1 Systemic anti-leprosy drugs.
2 Patient education about inflammation, its recognition, significance and need for treatment. Reinforce the need for compliance in taking anti-leprosy drugs.

CILIARY BODY

The earliest infiltrates probably start here. If the disease is very active, macroscopic nodules may form and grow to involve adjoining structures—the root of the iris and the overlying sclera.

SCLERA, EPISCLERA AND CONJUNCTIVA

The nodules which originate in the ciliary body appear on the surface near the temporal limbus (corneo-scleral junction) which is a cool, exposed part of the eye. They are painless. They have firm to rubbery texture and are pink to yellow in colour. They may extend into the cornea. Large nodules can interfere with the normal function of the eyelids in spreading the tears over the corneal surface. Nodules suggest very active disease. Their appearance, after anti-leprosy treatment has been fully established, suggests either *non-compliance*, a *non-effective drug* or *drug resistance.*

Management

1 Systemic anti-leprosy drugs.

2 Superficial excision of large nodules to restore normal eyelid function. (This surgery requires trained personnel.)
3 Patient education about the need for compliance in taking anti-leprosy medications as ordered, and a warning about possible inflammation.

INFLAMMATION OF THE EYE INFILTRATED WITH LEPROSY BACILLI

This is the ocular counterpart of erythema nodosum leprosum (ENL) of the skin, and like ENL, it is a recurring phenomenon. It occurs only in the lepromatous form of the disease. Remember that there is a mycobacterial infiltration of the eye without inflammation which was just reviewed. The time interval between infiltration and inflammation may be as little as a few months, but could be as much as several years after the initial infiltration of the eye. This may occur when the bacterial index is declining but the antigen level is apparently high. It may continue to occur after the disease is 'inactive' by current criteria. It must be understood by personnel who treat the eye, that the eye contains very reactive tissues and often requires much longer periods of time to subdue inflammation and infection than other structures in the body such as the skin.

The structures affected are the iris and ciliary body (iritis, iridocyclitis or 'anterior' uveitis), episclera (episcleritis) and sclera (scleritis).

Note. The cornea is not affected unless previously vascularized.

Warning

If the sensation of pain is impaired, symptoms are unreliable. Therefore, objective examinations are mandatory. The patient must practice monitoring of his own visual acuity. It may be his only index of trouble.

EPISCLERITIS

Diagnosis and symptoms

Moderate pain especially on eye movement.

Signs

Redness, usually in discrete patches, Dull red. Patches are *very tender*. (Palpate these patches through the eyelids.) Retract the eyelids to examine fully all quadrants of the eye.

Management

Steroid drops. Apply them hourly, initially, then reduce the frequency as fast as

the condition permits. Steroid ointments are valuable for night-time use or when the condition is less acute. Warm-compresses are comforting and possibly therapeutic.

SCLERITIS

A serious complication which can lead to scleral perforation. It is less common than episcleritis. It may be associated with intraocular inflammation.

Diagnosis and symptoms

Severe deep pain. Distribution of the pain is circumorbital and radiating back to the temple.

Signs

Redness, with mauve to grey tinge. Usually in discrete patches. Distribution is varied but commonly over the ciliary body area. Affected areas are *exquisitely tender*. The diagnosis can be made by a penlight and gentle palpation through the eyelid.

Complications

Scleral thinning or actual perforation. Appear later as slate-grey areas deep to the conjunctiva.

Management

1 Topical steroid drops are helpful, but inadequate if used alone.
2 Subconjunctival steroid injections.
Note: Do not inject in the immediate area of the inflammation. Use the soluble form of the drug, not the depot form. Personnel must be trained in the technique.
3 Systemic steroids and/or other systemic anti-inflammatory agents.
4 Analgesics and warm compresses for pain as required.

IRIDOCYLITIS (IRITIS, 'ANTERIOR' UVEITIS)

The principle single cause of blindness in leprosy

Intermittent attacks may occur over many years. Between the acute attacks or exacerbations, low-grade inflammation without symptoms may persist causing adhesions and later complications, e.g. secondary glaucoma. Other complica-

tions include cataract, iris and ciliary body atrophy and, finally, phthisis bulbi (soft, blind eye).

Diagnosis and symptoms

Decreased vision, pain of the whole eye, photophobia and tearing.

Signs

Eyelid swelling, *red eye, tender eye, ciliary flush (circum-corneal injection)*, corneal oedema (steamy), cloudy aqueous humour, keratic precipitates (deposits on the internal surface of the cornea), *poorly reactive small pupil*, posterior synechiae (adhesions of iris to lens), *irregular pupil* (especially on attempted dilation with mydriatics), iris atrophy (advanced cases), eccentric pupil (advanced cases). Increased intraocular tension in some cases.

Note: The entire anterior segment of the eye is involved to varying degrees. Signs written in italics are found frequently and are most easily recognized by the practitioner without the benefit of formal ophthalmic training or sophisticated equipment.

Management

1 Effective anti-leprosy treatment.
2 Atropine eye drops or ointment twice a day.
3 Steroid eye drops or ointment. Use drops hourly, initially. Reduce frequency as fast as continuing control permits. Use ointment two to four times a day.

Note: Drops are generally more effective, easier to explain to the patient, and more economical as there is less waste. If the patient has trachoma or corneal disease also, use an appropriate topical antibiotic.
4 Systemic steroids if the uveitis is severe. Start with prednisone 60 mg per day and taper the dosage over approximately 2 weeks in most cases. Use for longer if indicated. (Thalidomide is a useful adjunct provided proper precautions are taken for female patients of child-bearing age.)
5 Subconjunctival steroid injection if the uveitis is severe. (One needs instruction to administer this injection.)
6 If the intraocular tension is elevated, use acetazolamide (Diamox) 250 mg four times a day. (Do not use pilocarpine. It counteracts atropine.)
7 Intraocular tension needs to be monitored at least bi-weekly while uveitis is active, or while steroids are being used topically. (Steroid-induced glaucoma can occur.)

EXTRA-OCULAR INVOLVEMENT: MADAROSIS

Pathophysiology. Destruction of hair follicles by leprosy bacilli.

Diagnosis

Loss of eyebrows and/or eyelashes.

Management

1 Systemic leprosy treatment.
2 Cosmetic eyebrow transplants from the scalp.

Note. The hair loss is permanent; however, a hair transplant will take if done properly. A neuro-vascular island pedicle flap is one of the best procedures.

DACRYOCYSTITIS—PATHOPHYSIOLOGY

Obstruction of the naso-lacrimal duct secondary to destruction of nasal mucosa and nasal bone absorption. May be acute, progressing to abscess formation, rupture and fistula formation. More commonly it presents as low-grade infection, symptomless except for some swelling and a chronic watery, muco-purulent discharge in the conjunctival sac. This chronic source of infection, often overlooked, is a potential danger to the cornea already compromised by exposure and the increased risk of trauma. Corneal ulceration is then a probability. It also increases the risk of postoperative ocular infection in eyes subjected to surgery. Endophthalmitis may ensue in intraocular surgical cases.

Diagnosis, symptoms and signs

Acute infection

Pain, swelling, tenderness (maximal in the lacrimal sac area), lacrimation with or without purulent exudate.

Chronic infection

Lacrimation with purulent exudate increased by pressure over the lacrimal area. Slight swelling and tenderness. Obstruction to irrigation of the naso-lacrimal system.

Management

For the acute condition:
1 Hot compresses.
2 Systemic antibiotics.

For the chronic condition:
1 Gentle digital expression of the pus through the puncta. If it does not come readily do not force it. The canaliculi (between the puncta and lacrimal sac) may also be obstructed.
2 Daily irrigation of lacrimal sac using saline then antibiotic ophthalmic solution, for 2 weeks.

3 Dacryocystorrhinostomy if indicated.
4 Dacryocystectomy, if indicated. If the nasal mucosa is unhealthy this may prove to be the better procedure.

Note. Dacryocystorrhinostomy and Dacryocystectomy should be done by a surgeon knowledgeable in these procedures.

Examination of the eye in leprosy

When examining the eyes of a person with leprosy, it is important to remember that he may have other conditions of the eyes not necessarily associated with leprosy; e.g. trachoma, cataracts, glaucoma, conjunctivitis, vitamin and nutritional deficiencies, significant refractive errors, etc. *Just because leprosy is present, do not assume every abnormality is due to leprosy.*

The following is a quick, simple, step-by-step eye examination of a patient with leprosy. If done properly, the vast majority of eye problems—both due to leprosy and other causes—should be diagnosed.

1 Observe patients for spontaneous blink (5th nerve). Is it frequent enough and symmetrically complete?
2 Ask the patient to close his eye 'as in sleeping' and with maximal effort (7th nerve).
3 Examine the conjunctiva and cornea with a penlight (external diseases).
4 Check pupillary reaction with the penlight at the same time (iris atrophy, posterior synechiae due to uveitis).
5 Palpate the eye through closed eyelids to check for tenderness (scleritis, uveitis).

Note. Steps 1–5 required a penlight as the only piece of equipment. In most cases, 25–30 seconds per patient is adequate time for these steps.

The following two steps are more involved and should be done if possible:
6 Record the vision. With minimal training, an assistant can test the vision for the clinician to save time. Vision chart is required.
7 Intraocular pressure. This can be tested by a well-trained assistant. Requires a tonometer and a place for the patient to lie down. Clean the tonometer between patients. (If alcohol is used be sure to wipe the tonometer dry before using it again as alcohol can cause a painful keratitis.)

Conclusion

Ocular leprosy is a complicated medical condition; however, if the practitioner will use the information outlined in this paper and examine the eyes of many leprosy patients, he will find that the diagnosis and proper management of ocular leprosy is logical and attainable.

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Incubation time of relapses after treatment of paucibacillary leprosy

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Accepted for publication 18 August 1983

Summary Data are presented on the incubation time of 21 relapses after stopping dapsone monotherapy in paucibacillary leprosy in Central Africa. The results are comparable with those of other studies: 50% of relapses occur during the first 2–3 years. This figure is most important to analyse the results of drug trials in paucibacillary leprosy. This figure should also be relevant for regimens including more bactericidal drugs than dapsone, since the kind of antibacterial treatment should influence the minimal necessary duration of treatment but not the incubation time of relapses.

The same mechanisms prevailing in relapses of multibacillary leprosy, their incubation periods should be identical.

The two most important criteria for the evaluation of treatment regimens in infectious diseases are improvement or disappearance of symptoms, as evaluated by clinical, bacteriological, histopathological and other procedures, and incidence of relapses. For the organization of studies of treatment regimens it is most important to know the length of the incubation time of relapses, since this should determine the duration of the follow-up period after treatment has ceased. In studies on the treatment of pulmonary tuberculosis, originally, follow-up periods of 2 years were chosen, but later reduced to 1 year, when it became apparent that most relapses, after stopping treatment, appeared during the first year.

Now that similar treatment trials are envisaged in leprosy, it is equally important to gather information on incubation times of relapses in leprosy. We

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0305-7518/84/055115+06 $01.00

present here the results of our Study Group concerning the incubation time of relapses during the last 2 years in Central Africa: Zaire, Rwanda and Burundi, and compare them with similar data from the literature.

Materials and methods

In the whole of Rwanda and Burundi, and in parts of Zaire, Collaborating Centres are based in rural hospitals and visit peripheral dispensaries and health centres at intervals of 1, 2, 6 or 12 months. Patient detection is passive.

For each patient not under treatment, a case history is taken, and clinical and bacteriological examinations are performed and recorded on standard clinical files, copies of which are forwarded to the Leprosy Laboratory, Institute for Tropical Medicine, Antwerp, together with a skin biopsy if the patient has a paucibacillary (PB) form of the disease (paucibacillary leprosy being characterized by a bacterial index of less than two at any of at least three skin smears taken either from one earlobe and two skin lesions or two earlobes and one skin lesion).

The data are analysed in Antwerp. A relapse is defined as the appearance of new skin lesions, confirmed as leprosy through either bacteriology or histopathology, in a patient for whom clinical files are available documenting the previous diagnosis, and considered cured by a medical doctor or an experienced

Table 1. Incubation time for relapses after treatment of paucibacillary leprosy

Incubation time*	No.
2/12	1
6/12	1
9/12	2
1	3
1 4/12	1
2	2
3	3
4	1
5	2
6	1
8	1
20 and more	3

* In years or fractions thereof.

paramedical worker who had deliberately taken the decision to stop treatment. In French-speaking African countries the expression '(E)OST (en) observation sans traitement' (under observation without treatment) is currently used. Thus were excluded, patients who presented themselves after absconding and claiming they had new lesions, and patients who claimed they had been cured in the past but for whom no clinical files, testifying the anamnestic data were available.

In the present study relapses are not related to a well-defined population of previously treated patients but were noted as they presented spontaneously. All patients had been treated with dapsone monotherapy mostly in increasing dosages at the start, and maintained on dapsone 50 or 100 mg daily, in self-administration.

Results

A total of 21 paucibacillary relapses were documented.

The incubation times (Table 1) varied from 2 months to 20 years and more, with a mean of 5 years, Figure 1. Based on an underlying exponential distribution of the relapse times, the median was calculated as $3\frac{1}{2}$ years. The 95% confidence intervals, based on the variance calculation by Greenwood's formula and a

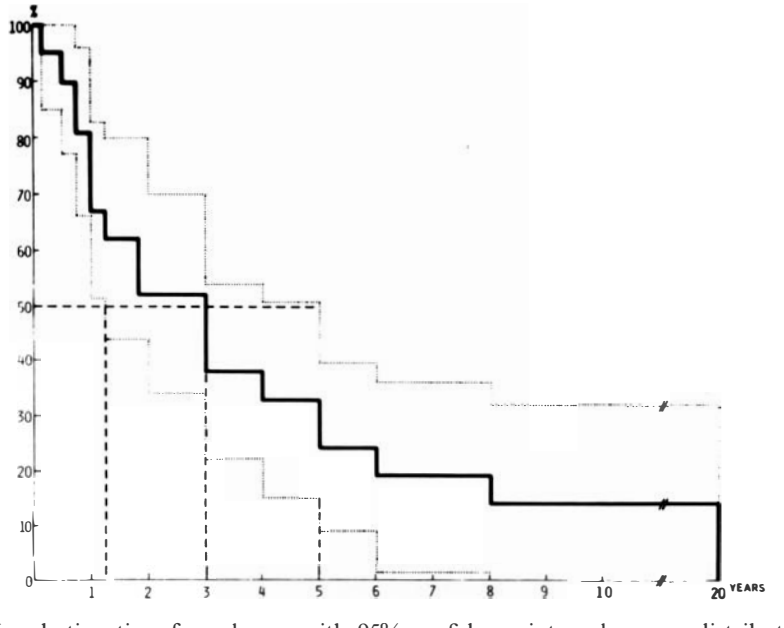

Figure 1. Incubation time for relapses with 95% confidence intervals. ——, distribution of the relapse incubation times; ------, 95% confidence intervals of the distribution of the relapse incubation times.

bilateral hypothesis, are represented graphically in Figure 1, and are situated between $1\frac{1}{4}$ and 5 years.

There was no correlation between the duration of previous, unsupervised, dapsone therapy and the incubation time for relapse. The minimum duration of therapy was 2 years (1 case) but most patients had been treated for 5 years or more, but since treatment was not supervised the actual intake of drug is unknown.

All cases had originally been diagnosed and classified as PB leprosy. At relapse, 17 were classified histologically as BT and 4 as TT leprosy, the incubation times for relapse in the latter were 2 and 5 months and 2 and 5 years respectively.

Discussion

For the evaluation of the efficacy of treatment regimens in leprosy, figures are urgently needed on the incubation time of relapses after stopping treatment, to allow the determination of the minimal necessary duration of follow-up. There are not so many data on this subject in the literature and most are concerned with multibacillary leprosy, whereas for PB leprosy the aim of most studies was to define the length of dapsone treatment necessary to prevent relapses.

In 1954, Lowe[1] mentions that in a group of patients followed for periods from a few weeks to 4 years—on average 22 months—8 relapses were observed. Seven occurred between 3 and 12 months and one 28 months after stopping treatment.

In a study[2] on 34 relapses of PB leprosy, the mean incubation time for relapse was 2·73 years and the median 2·7 years, with a 95% confidence limit between 1 and 2 years and 3 years; 55% of relapses occurred within the first 3 years of follow-up. The confidence intervals determined in our study are of the same order of magnitude, although somewhat larger, this might be due to the smaller sample size of our study group.

In a study of 105 relapses[3] in PB leprosy patients followed during $3\frac{1}{2}$ years, note that 75% of them were diagnosed within the first 2 years after stopping treatment.

Another study[4] was also aimed at defining the optimal duration of therapy but the information necessary for the present purpose can be derived from their figures. In this study, 48% of relapses after stopping treatment occurred during the first 2 years, the 95% confidence limit of this figure being between 0 and 4·1 years.

Differences between the studies mentioned are the duration of follow-up and the diagnostic criteria. Follow-up was shorter in two studies, average 22 months,[1] and $3\frac{1}{2}$ years,[3] than in the other studies. Depending on the shape of the curve, a greater fraction of the total number of relapses may appear earlier after discontinuation of treatment, as was the case in the two above-mentioned studies.

Diagnostic criteria may also differ between clinicians, particularly for

paucibacillary leprosy, where the criteria for 'activity' are rather ill defined and are somewhat subjective. However, in each study mentioned the same clinicians were responsible for the diagnosis of relapse and in the present study the more objective histopathological criterion was used. Furthermore, the frequency at which patients are seen or may be seen, particularly in ambulatory services, may also determine the moment at which a relapse is diagnosed or may possibly be diagnosed.

But in conclusion it may be stated that during a follow-up period of 3 years after stopping treatment in PB leprosy, 50% of relapses should be observed.

One may wonder whether relapses observed shortly (within less than 1 year) after stopping a treatment of short duration are real relapses or upgrading reactions. Only careful future studies will perhaps be able to answer this question.

It is sometimes argued that late relapses occurring many years after stopping treatment may be the result of reinfections and thus are not necessarily relapses. This is certainly true but impossible to prove or disprove. Therefore, it is preferable for the calculation of the incidence of relapses to adopt the 'worst' hypothesis and consider them as relapses.

Another argument frequently raised during discussions is that all data presently available are from patients treated with dapsone monotherapy and that these figures could be entirely irrelevant when powerful bactericidal drugs such as rifampicin and/or ethionamide are used. This results from a confusion of two different issues. One is the antibacterial treatment, aimed at the killing of the etiological miroorganism, the other is the time necessary for viable microorganisms, subsisting after the end of the antibacterial treatment, to multiply again to such a level that new clinico-pathological lesions appear. The minimal duration of the antibacterial treatment necessary to kill all responsible microorganisms will certainly differ for drugs with differing bactericidal activity. However, the incubation time for relapses is a function of the presence of viable organisms present at the end of the antibacterial treatment, their number and the immunological defence capability of the host. However, the generation time of the bacilli is unaffected by the drugs previously administered.

Thus a clear distinction should be made between the incidence of relapse and the kind and duration of antibacterial therapy. The latter will certainly influence the incidence of relapses but not their incubation time. This is so in all infectious diseases in general and in tuberculosis in particular: the incubation time for relapses is not influenced by the drugs previously administered. The main difference between leprosy and tuberculosis in relation to the incubation time of relapses is that in the latter 90% appear within the first year after stopping treatment, whereas in leprosy only 50% are diagnosed within the first 3 years. This is most probably related to the widely different generation times of the two etiological agents. After stopping treatment one viable *Mycobacterium tuberculosis* needs about a month to grow out to a population of $10,^{7}$ while one viable *Mycobacterium leprae* needs 1 year. The possibly greater natural immunity of

humans against *M. leprae* may, furthermore, delay the appearance of clinical disease in this infection.

And the same rules also hold for multibacillary leprosy: relapse being a function of the existence of viable organisms at the end of treatment, their unaltered generation time in the absence of antileprosy drugs and the lower antileprosy immunity of the patient as compared with paucibacillary leprosy, 50% of relapses in multibacillary leprosy should also appear within 3 years after stopping treatment. We hope that future studies will clarify this point.

Acknowledgments

This study was made while the Leprosy Laboratory of the Institute of Tropical Diseases, Antwerp was financed by the Damien Foundation, Brussels, Nationaal Fonds voor Wetenschappelijk Onderzoek, Brussel and the Chemotherapy of Leprosy (Thelep) component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. A. De Muynck performed the statistical calculations.

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Lepr Rev (1984) **55,** 121–128

A study of thiacetazone blood levels and urinary excretion in man, using high performance liquid chromatography

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Accepted for publication 8 September 1983

Summary The pharmacokinetics of thiacetazone, a bacteriostatic drug with both antituberculosis and antileprosy activity, have been studied in healthy volunteers and tuberculosis patients using a high pressure liquid chromatographic method. Urinary excretion of thiacetazone was measured over a period of 7 days following the ingestion of a single oral dose of 150 mg of the drug. Peak plasma concentrations of thiacetazone during supervised daily treatment averaged 1·8 μg/ml. From the rate of decline of thiacetazone plasma concentrations and urinary excretion, it was calculated that thiacetazone concentrations capable of inhibiting the multiplication of *Mycobacterium leprae* would only be maintained for about 3 days in the event of patients discontinuing to take the drug. It was concluded that thiacetazone cannot be recommended for use in the multi-drug treatment of lepromatous leprosy.

Introduction

The clinical activity of thiacetazone (TB1, thioacetazone, *p*-acetylamino-benzaldehyde-thiosemicarbazone) in the treatment of leprosy was first described 30 years ago,[1] while its efficacy when combined with isoniazid for the treatment of pulmonary tuberculosis was demonstrated in a series of controlled clinical trials carried out in East Africa during the 1960s.[2, 3] TB1 continues to be the only commonly available companion drug to isoniazid for use in many Third World countries where the recommended standard treatment for tuberculosis is often 12–18 months' daily isoniazid plus TB1 together with an initial supplement of up to 8 weeks' streptomycin.[3, 4] When TB1 was first used in the treatment of leprosy it was given alone and many patients eventually relapsed, presumably due to the selection of thiacetazone-resistant organisms.[5, 6]

The recent search for drugs of potential use in the multi-drug treatment of lepromatous leprosy which has been stimulated by the increasingly serious

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problem of dapsone resistance, has led to an experimental evaluation of the antileprosy activity of TB1.[7–9] Mouse foot-pad studies have confirmed that TB1 inhibits the multiplication of *Mycobacterium leprae*. Its minimal inhibitory concentration (MIC) was estimated to be about 0·2 μg/ml. However, its activity was primarily bacteriostatic and when TB1 was administered once-weekly its efficacy was substantially impaired.[9] It is known that leprosy patients may ingest their prescribed daily TB1 treatment very irregularly. Thus, in a study carried out in Ethiopia, urine tests demonstrated that only about 30% of the patients had swallowed their TB1 dose within the previous 48 h.[10] Such findings indicate that poor compliance could seriously limit its therapeutic efficacy, particularly if TB1 were rapidly eliminated so that inhibitory levels were not maintained for very long.

Previous estimates of the concentrations of TB1 achieved in the serum after the ingestion of therapeutic doses of the drug (150 mg) were often imprecise because the methods available in the past for its determination were relatively insensitive, non-specific and inaccurate.[11] Thus none of the published ultraviolet or fluorimetric methods[12, 13] were capable of measuring TB1 concentrations below its MIC against *M. leprae* and hence were incapable of directly assessing the duration during which inhibitory concentrations are likely to be maintained after standard dosage. Recently we devised a sensitive and specific high-performance liquid chromatographic (HPLC) method for determining TB1 in plasma and urine and reported preliminary studies on its pharmacokinetics in a single volunteer.[11] This paper describes its application to more extensive studies in a group of healthy volunteers and in tuberculosis patients.

Methods

CHEMICALS

HPLC-grade acetonitrile was purchased from Rathburn Chemicals (Walkerburn, Peebleshire) and other chemicals and solvents were of analytical grade from BDH Chemicals (Poole, Dorset). TB1 was donated by Smith and Nephew (Harlow, Essex) and recrystallized from ethanol. 4-Propylamino-benzaldehyde-thiosemicarbazone (PBT), the propionyl analogue of TB1, was used as the internal standard. Its synthesis has been described elsewhere.[11] Stock solutions (1 mg/ml) of the two thiosemicarbazones were prepared in ethanol and stored at 4°C. Standard curves were prepared by adding appropriate amounts of TB1 and the internal standard to either blank urine or plasma.[11]

PATIENTS AND SAMPLES

The investigation was divided into two parts. Twelve healthy members (2 female,

10 male) of the Medical Research Council's Unit for Laboratory Studies of Tuberculosis and the Royal Postgraduate Medical School Bacteriology Department, aged 19–49 years and weighing 57–95 kg participated in the first study after giving their informed consent. After emptying their bladders, the volunteers swallowed a single capsule containing 150 mg thiacetazone plus 100 mg dapsone plus 6 mg isoniazid[14] some 3 h after a light breakfast and 2 h before lunch. Complete urine collections were then made at 2-hourly intervals up to 6 h and thereafter 1-hour collections from 23·5–24·5, 47·5–48·5, 119·5–120·5, 143·5–144·5 and 167·5–168·5 h. Aliquots of urine were stored at −20°C prior to analysis.

The second study was carried out in 15 tuberculosis patients (3 female, 12 male) from the Infectious Diseases Hospital, Nairobi, Kenya (ages 17–45 years, weights 37–66 kg), undergoing treatment with daily streptomycin (1 g), isoniazid (300 mg) and TB1 (150 mg), their renal and hepatic functions were normal. For the purposes of the study, five consecutive daily doses of the drugs were given under full supervision and food was withheld for 12 h before the last supervised dose to ensure it was taken on an empty stomach. Blood samples (10 ml) were collected immediately prior to the ingestion of this final TB1 dose, then 2, 4, 6 and 24 h afterwards. A light breakfast was taken after the second blood sample. Blood was taken into heparinized tubes and spun down within 1 h of collection. The plasma was then transferred to polypropylene tubes, rapidly frozen and stored at −20°C prior to analysis in London.

ANALYTICAL PROCEDURE

The method employed to extract the samples has been described in detail elsewhere.[11] Briefly, after adding 6 μg of the internal standard (PBT) and 1 M pH 7 phosphate buffer, plasma or appropriately diluted urine samples were extracted with ethyl acetate. Then, after washing with 0·1 M sodium hydroxide, the organic extract was evaporated to dryness under nitrogen. HPLC analyses were performed using a Waters Associates (Northwich, Cheshire) Model M6000A pump, Model 440 ultraviolet detector set at 313 nm and U6K septumless universal injector. A reverse phase system was used consisting of a 25 cm × 5 mm internal diameter 5 μ ODS Hypersil column (Shandon Southern, Runcorn, Cheshire) with a mobile phase of acetonitrile/water (3 : 7 by volume) delivered at a flow-rate of 1·5 ml/min. The minor modifications in the chromatographic method from that published elsewhere[11] were primarily introduced to permit the simultaneous determination of dapsone in the urine samples from the volunteers who received the combined dose (Jenner & Ellard, unpublished results). Neither dapsone, streptomycin, isoniazid or its metabolites acetylisoniazid and isonicotinic acid interfered with the determination of TB1.

Dried urine extracts were dissolved in 100 μl of the mobile phase, duplicate 25-μl aliquots injected and the mean ratio of the peak heights of TB1 to that of the internal standard calculated. Dried plasma residues were extracted by shaking

with 100 μl of the mobile phase together with 100 μl of 2% ethanol in n-hexane in order to remove interfering lipophilic components. After centrifugation, 25-μl aliquots of the lower aqueous phase were injected.

Calibration curves were prepared by spiking blank urine and plasma with TB1 to give concentrations of 0, 0·2, 0·5, 1 and 2 μg/ml, respectively. Duplicate 3-ml aliquots were extracted and chromatographed as described above after the addition of 6 μg PBT. The equations of the lines relating mean peak height ratios of duplicate injections to concentration of TB1 were linear, and the best straight lines and standard errors of slopes and intercepts were calculated by the least squares method.

Results

A representative chromatogram of a plasma extract obtained 2 h after the final supervised dose of 150 mg TB1 from a patient in the East African study is shown in Figure 1. Plasma and urinary concentrations of TB1 were calculated from the peak height ratios of TB1 to PBT and the calibration curves whose equations are given in Table 1 together with the standard errors of the slopes and intercepts. Neither of the intercepts differed significantly from zero. Replicate errors

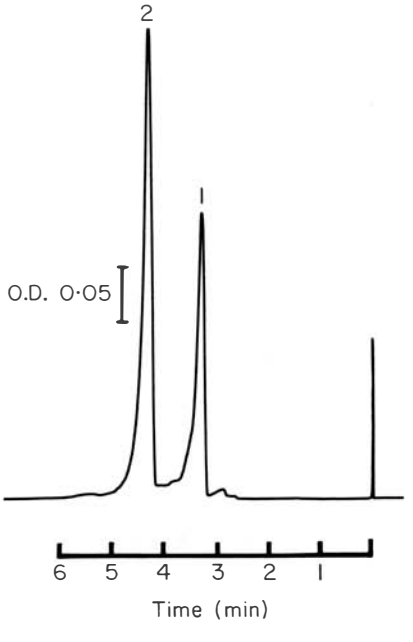

Figure 1. Chromatogram of an extract of plasma from a tuberculosis patient 2 h after the ingestion of the fifth consecutive supervised daily dose of 150 mg TB1 plus 300 mg isoniazid plus 1 g streptomycin. Peaks: (1) TB1; and (2) PBT (the internal standard).

Table 1. Equations* of calibration curves

Biological fluid	Concentration range (μg/ml)	Slope ±s.e.†	Intercept ±s.e.
Urine	0·2–2·0	0·636±0·004	0·012±0·004
Plasma	0·2–2·0	0·636±0·008	0·014±0·009

* Equation $y=mx+c$, where y is the ratio of the peak height of TB1 to that of the internal standard, m is the slope, and x the concentration of TB1.

† Standard error.

calculated from the calibration curves averaged 1·2% for urine and 3% for plasma.

The mean rates of urinary excretion of unchanged TB1 by the 12 healthy volunteers over the 7-day period following the oral ingestion of single 150 mg doses of TB1 are illustrated in Figure 2. Urinary excretion of TB1 diminished more rapidly during the first day (half-life equivalent to 14 h over the period 5–24 h), confirming the biphasic decline encountered in the previous investigation on a single volunteer.[11] From 24 h onwards the apparent half-life for the urinary excretion of TB1 by the 12 volunteers averaged 21·5 h (range 15·8–37·6 h).

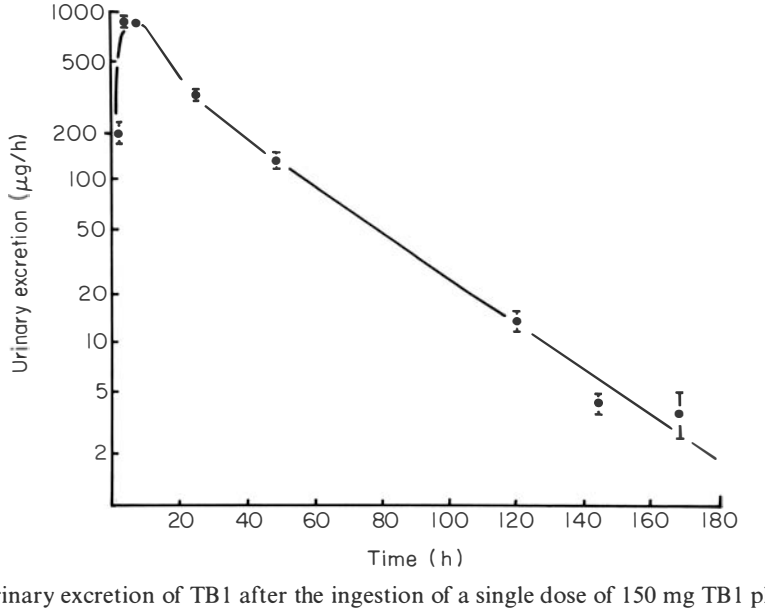

Figure 2. Urinary excretion of TB1 after the ingestion of a single dose of 150 mg TB1 plus 100 mg dapsone plus 6 mg isoniazid. Points represent geometric means and bars show standard errors for the 12 healthy volunteers.

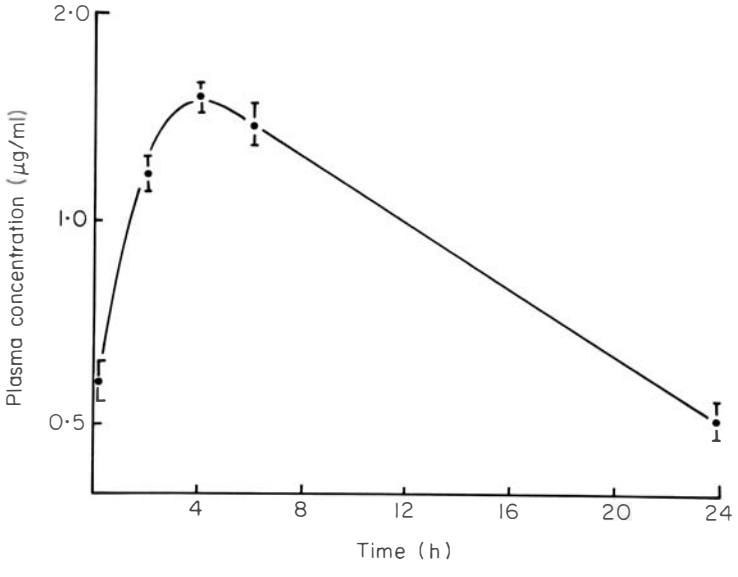

Figure 3. Plasma concentrations of TB1 after the ingestion of the fifth consecutive supervised daily dose of 150 mg TB1 plus 300 mg isoniazid plus 1 g streptomycin. Points represent geometric means and bars show standard errors for the 15 tuberculosis patients.

However, only one of the volunteers had a TB1 half-life over this period in excess of 28 h, a value significantly longer ($P < 0{\cdot}001$) than that of 11 others whose TB1 half-lives did not differ significantly ($P = 0{\cdot}2$).

The mean plasma TB1 concentrations of the 15 tuberculosis patients following the ingestion of the last of the five consecutively supervised daily doses of 150 mg TB1 are illustrated in Figure 3. Peak TB1 concentrations averaged 1·76 μg/ml and were attained within 4 h in all but three of the subjects. From 6 to 24 h TB1 plasma concentrations declined at a rate equivalent to a half-life of 12·9 h. Plasma TB1 concentrations at 0 and 24 h did not differ significantly ($P > 0{\cdot}25$). They averaged 0·65 (SD 0·32) and 0·55 (SD 0·26) μg/ml, respectively. Although an analysis of variance showed that there were significant interindividual differences between patients in their trough TB1 plasma concentrations ($P < 0{\cdot}005$), such differences could not be accounted for by differences in age or weight.

Discussion

A recently devised specific and sensitive HPLC method[11] has been applied to determine the plasma concentrations of TB1 in tuberculosis patients and rates of its urinary elimination in healthy volunteers. This has provided accurate information to assess the potential of the drug when employed as a component of

multi-drug regimens for the treatment of lepromatous leprosy. Peak and trough plasma concentrations of TB1 after daily dosage with 150 mg of the drug averaged 1·76 and 0·60 μg/ml respectively. These mean values are similar to those obtained in an earlier investigation carried out on a large number of tuberculosis patients from Kenya and Singapore using less sensitive and specific ultraviolet and fluorimetric methods.[13] The peak and trough concentrations of TB1 only exceeded its MIC against *M. leprae* by about 9- and 3-fold respectively. When given at a daily dosage of 150 mg, serum concentrations of thiacetazone were unaffected by the co-administration of 1 g streptomycin,[13] while the rate of its urinary excretion was uninfluenced by giving 100 mg dapsone concomitantly (Jenner and Ellard, unpublished results).

From the decline in the rates of TB1 urine excretion beyond 24 h, it may be calculated that inhibitory levels of the drug would only be maintained for about 3 days following cessation of regular daily treatment, a conclusion supported by the study carried out on a single healthy volunteer.[11] This study therefore confirms the previous conclusion[10] that poor compliance would seriously impair the therapeutic efficacy of this inherently weak bacteriostatic drug and that as a consequence TB1 cannot be recommended for general out-patient use in the multi-drug treatment of lepromatous leprosy.[15, 16]

Acknowledgments

This study was undertaken under the joint auspices of the Kenya Medical Research Institute and the British Medical Research Council. We are indebted to Dr Jan Mohammed, Mr Eric Edwards and Mr Robert Thiong'o for their assistance. Our thanks are also due to the volunteers and patients for their participation in the investigation.

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The association of pregnancy and leprosy—III. Erythema nodosum leprosum in pregnancy and lactation

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Accepted for publication 11 October 1983

Summary Seventy-six women with lepromatous leprosy were studied during 79 pregnancies and followed up during lactation for up to 24 months. Ten out of 45 BL patients (22%) and 20 out of 34 LL patients (59%) developed erythema nodosum leprosum (ENL) during the course of the study. Only 4 out of 30 patients were BI negative, although the duration of effective treatment for leprosy ranged from 1 to 14 years. Thirteen of the 30 ENL patients were suspected of developing dapsone resistance during the study period. The incidence of ENL was highest in the first trimestre with a second peak in the third trimestre, coinciding with the peak of relapse. Fifteen per cent of the women suffered from ENL almost continuously from the third trimestre to 15 months postpartum. In pregnancy ENL was seen more frequently in skin than in nerve or other tissue; however, after delivery, particularly in the recurrent or persistent episodes, ENL was seen more commonly in nerve than in skin. Significant sensory and/or motor loss occurred in 30 out of 38 episodes of ENL nerve involvement. The significance of these findings is discussed.

Introduction

Erythema nodosum leprosum (ENL) has been considered to be a form of immune complex disease characterized by the deposition of immunoglobulin and complement in the vicinity of *Mycobacterium leprae* antigen.[1–3] Tissues affected in decreasing order of frequency are skin, nerve, lymphnodes, joints and other sites.[4] Immune complexes have been detected by the precipitation of C_{1q} in a high percentage of sera from patients with ENL.[5] However, the actual role of immune complexes in the immunopathology of ENL remains to be elucidated.[5, 6] Recently it has been suggested that depletion of suppressor T-cells may be responsible for the initiation of ENL.[7]

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ENL is seen chiefly in patients with lepromatous (LL_p or LL_s)[8] leprosy, where more than 50% of patients may experience ENL during the first year of treatment.[9] It occurs less frequently in patients with borderline lepromatous (BL) leprosy.

Factors which increase the levels of antigen, antibody or complement could well affect or precipitate ENL. A number of such factors are associated with pregnancy:

(a) During the first trimestre of pregnancy there is inversion of the T-cell: B-cell ratio due to physiological depletion of suppressor T-cells;[10] this might be related to the development of ENL at this time. (b) The increased level of circulating immune complexes (not specifically anti-mycobacterial) in late pregnancy[11, 12] may encourage the appearance of ENL at that time. (c) Pregnancy in leprosy is often associated with relapse in 'cured' patients, and with a tendency to increased activity in patients under treatment, accompanied by a shift towards the lepromatous end of the leprosy spectrum.[12, 13] All these are likely to be associated with an increase in levels of mycobacterial antigen; such an increase has been demonstrated even in patients relapsing with tuberculoid (BT) leprosy.[14]

It is hardly surprising that pregnancy has been suggested as a precipitating factor of ENL[15] and, indeed, recorded as such in retrospective studies.[16, 17] This paper reports the association of ENL with pregnancy and lactation as observed in a prospective study carried out by the Medical Research Council Leprosy Project in Addis Ababa, Ethiopia, during 1975–78.

Patients and methods

CLASSIFICATION AND TREATMENT OF PATIENTS

Seventy-six women with lepromatous leprosy were studied during 79 pregnancies and followed up during lactation. The classification according to Ridley & Jopling[18] was:

Borderline lepromatous leprosy (BL)—44 women (45 pregnancies).
Lepromatous leprosy (LL_p and LL_s)—32 women (34 pregnancies).

Sixty-five of the women (67 pregnancies) were receiving dapsone 100 mg daily, 4 under trial conditions[19] for suspected low-grade dapsone resistance; 6 women had dapsone-resistant leprosy and were receiving clofazimine 300 mg weekly (4 LL, 5 pregnancies) or triple therapy with dapsone, thiambutosine and rifampicin (2 BL). Five patients at the start of the study were not receiving any anti-leprosy treatment: 1 'cured' BL had been released from control (RFC) after 20 years of treatment; 3 initially classified as 'cured' borderline tuberculoid (BT/RFC) all relapsed with active BL leprosy during the third trimestre; 1 healthy control

developed overt leprosy during the first 3 months of lactation. The 'healthy control' new case, and 2 of the 3 BT/RFC patients were started on treatment with dapsone 100 mg daily as soon as active leprosy was diagnosed; the third BT/RFC failed to attend for follow-up and was untraceable after delivery.

SELECTION AND ASSESSMENT OF PATIENTS

Selection of patients was based chiefly on the patients' willingness to participate in the study. Assessment of the women's leprosy status was made on entry to the study, during pregnancy at 3-month intervals whenever possible, and after delivery at 6-monthly intervals. Full examination included inspection and palpation of the skin, peripheral nerves and regional lymphnodes, clinical drawings, skin smears and biopsies, sensory skin testing (SST) and voluntary muscle testing (VMT); nerve conduction velocity (EMG) was measured in selected patients where it was difficult to assess whether nerve damage was of old standing or recent origin. In the presence of obvious clinical changes (such as facial paralysis or 'tic' of the facial muscles; wasting of the intrinsic muscles of the hand; 'curving' of the fourth and fifth fingers; claw hand or foot drop), formal VMT's were sometimes omitted. Similarly, in a few patients with extensive anaesthesia with anhidrosis, formal SST's were omitted. These are reported as 'clinical assessments' (Table 1). Details regarding the patient's history and

Table 1. Severity of nerve damage during each episode of neuritis

Type of neuritis		Degree of nerve damage Motor* Mild	Motor* Severe	Sensory† Mild	Sensory† Severe	Total	No nerve damage detected (episodes)
Overt	One nerve only	1	1	0	0	2	8
	Many nerves	7	5	5	4	21	
Silent	One nerve only	1	1	2	1	5	
	Many nerves	2	6	3	4	15	
Total		11	13	10	9	43	8

* Mild damage: loss of one or two VMT grades in one or more nerves, or EMG evidence only.
Severe damage: loss of three or more VMT grades in one or more nerves, or clinical assessment only.

† Mild damage: loss of one or two sensory test areas in one or more nerves.
Severe damage: loss of three or more sensory test areas in one or more nerves, or clinical assessment only.

leprosy status prior to entry to the study were obtained from the hospital records. Full details are recorded in an earlier publication.[13]

INCREASED ACTIVITY OF LEPROSY ('RELAPSE')

Relapse was considered to have occurred where there was conversion of negative to positive BI or MI, where biopsy showed histological features of relapse with presence of acid-fast bacilli, solid staining, or where there were new nodules or skin infiltration not caused by reaction (histological diagnosis). Thirteen out of 21 had all 3 criteria, 2 had 2 criteria, 2 showed relapse on biopsy only, 1 showed conversion of negative to positive MI with rising BI, and 3 showed increase of BI only as a transient phenomenon during the third trimestre.[13] Patients continued to take dapsone throughout pregnancy; relapse was therefore considered likely to be caused by the emergence of dapsone-resistant leprosy.[19]

NEURITIS IN PREGNANCY AND LACTATION

We have used the term 'overt neuritis' for the accepted definition of neuritis as tender nerves with/without objective evidence of motor or sensory loss.[20] 'Silent neuritis' has been defined as loss of motor or sensory function without clinical evidence of nerve tenderness.[21] In both overt and silent neuritis there may be new nerve enlargement. When silent neuritis occurred in a lepromatous patient (BL or LL) who had ENL either at the same time or previously, we have regarded the silent neuritis as being due to ENL.

Results

Patients were admitted to the study over a 12-month period and followed up for varying lengths of time up to 24 months postpartum; the 3 months prior to pregnancy provided a baseline for the prevalence of complications of leprosy in women of child-bearing age. The incidence of ENL and increased activity of leprosy (relapse) are expressed as a percentage of the total number of women in the study in any 3-month period.

Thirty out of 79 patients (38%) developed ENL during the course of the study: 10 out of 45 BL patients (22%) and 20 out of 34 LL patients (59%). Twenty-nine of these patients had clinically diagnosable ENL in the skin on one or more occasions; the thirtieth, originally BT/RFC, developed iridocyclitis.

OCCURRENCE OF ENL IN ASSOCIATION WITH DURATION OF TREATMENT (FIGURE 1)

Fourteen patients (47%) had ENL within 4 years of the start of effective treatment

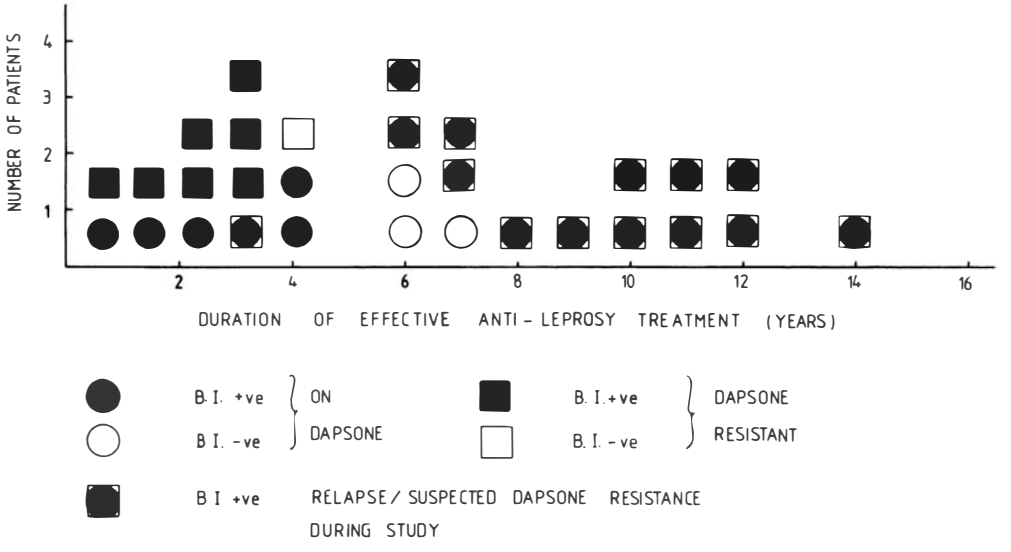

Figure 1. Duration of effective anti-leprosy therapy in 30 patients who developed ENL in association with pregnancy and lactation.

for leprosy, either initial treatment with dapsone, or dapsone under trial conditions (3 out of 4 patients already having evidence of suspected dapsone-resistant leprosy),[19] or alternative therapy in the case of 4 out of 6 dapsone-resistant patients (5 out of 7 pregnancies). All but one of these were BI positive. The remaining 16 patients showed ENL after 6–14 years of treatment with dapsone. Only 3 were BI negative. Two patients who had been on treatment for 11 years and were BI positive, had had 2–3 years of additional treatment with clofazimine for persistent ENL. Thirteen of the 30 patients were suspected of developing dapsone resistance during the study period.

TIMING OF FIRST EPISODES OF ENL DURING THE STUDY

The periods during which patients developed their first episodes of ENL during the study are shown in Figure 2(b). The incidence was highest during the first trimestre with a fall in the second, then a rise in the third, coinciding with the peak of relapse. There was a steady decline during lactation, only 2 cases starting after 9 months. However, when all patients suffering from ENL during a period are recorded (Figure 2(c)), it can be seen that a high proportion of patients with ENL have it persistently for many months after delivery; indeed, 15% of the group studied suffered from ENL or neuritis for the 18-month period from the third trimestre to 15 months postpartum. While the highest incidence of onset of ENL was during the first trimestre, before the women had realized they were pregnant and thus were attending the hospital clinics rather than the special clinics for this study, it is unlikely that ENL was either under-diagnosed or over-diagnosed:

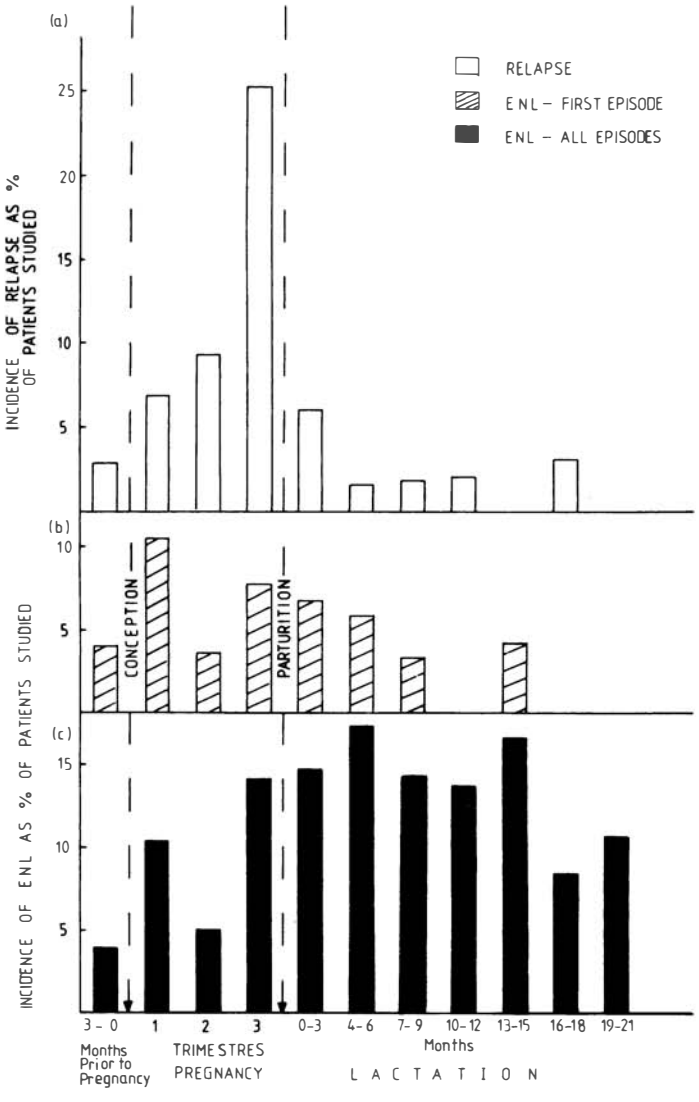

Figure 2. Percentage of patients: (a) showing evidence of relapse; (b) developing ENL (first episode); (c) suffering from ENL (all episodes) during each trimestre of the study period.

most patients with troublesome ENL attended hospital specifically on that account and the hospital doctors who saw them were leprologists of repute. Only 6 of the women suffered from persistent ENL lasting for 6 months or more: a larger proportion suffered from recurrent episodes of ENL.

ENL AND TISSUES INVOLVED, ACCORDING TO PREGNANCY AND LACTATION

During the 3 months prior to pregnancy, ENL was recorded only in the skin.

Throughout pregnancy ENL was seen more in the skin than in nerve or other tissue; however, after delivery, particularly in the recurrent or persistent episodes, ENL was seen more commonly in nerve than in skin (Figure 3). This was especially the case after the ninth month of lactation. Four patients (6 episodes) had evidence of ENL occurring in tissues other than skin or nerve; 2 episodes involved the eye, 2 episodes involved bone—both women had very tender tibiae and dactylitis, 2 had arthritis with concomitant nerve and/or skin ENL. All 4 women had ENL in association with relapse. Three other women had gross peripheral oedema in association with skin ENL. Six women had ENL in association with upgrading (5) or reversal reaction in skin (1) confirmed histologically.

ENL AND CLINICAL FEATURES OF LEPROSY DURING PREGNANCY AND LACTATION

Symptoms and clinical features of mothers who had ENL are shown in Table 2. Table 3 shows the symptoms and clinical features of mothers who did not have ENL.

The total duration of treatment in the patients who had ENL was rather longer than in those who did not have ENL: the period of effective treatment, however, was shorter, due to the inclusion of patients who had already developed dapsone resistance. All clinical features, except reversal reaction in BL patients,

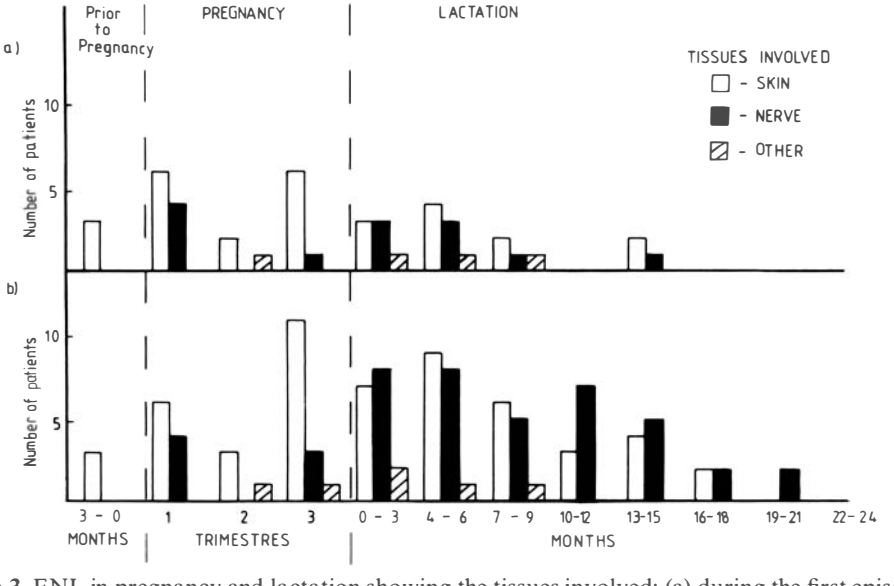

Figure 3. ENL in pregnancy and lactation showing the tissues involved: (a) during the first episode; (b) during all episodes, single, recurrent and persistent. (NB: In any single episode, one, two or more tissues may be involved.)

Table 2. Symptoms and clinical features in mothers who had erythema nodosum leprosum in pregnancy and lactation

Classif-ication	No. of women	Total duration of treatment (years) (Mean ±SEM)	Duration of effective treatment (years) (Mean ±SEM)	No. BI+ve	Increased activity of leprosy	Reversal reaction in skin (including histological up-and-down grading)	Enlarged nerves	Neuritis			Lymphad-enopathy	Complaint	
								Total No.	Overt	Silent		'Rheumatism'	Paraesthesiae
BL	10	7·93 ±1·25	7·15 ±1·47	9 (90%)	7 (70%) (1)‡	3 (3%)	8 (80%)	8* (80%)	6 (60%)	4 (40%)	6 (60%)	9 (90%)	2 (20%)
LL	20	7·85 ±0·78	5·58 ±0·7	17 (85%)	14 (70%) (6)‡	3 (15%)	10 (50%)	13† (65%)	8 (40%)	6 (30%)	13 (65%)	16 (80%)	3 (15%)
Total	30	7·88 ±0·66	6·1 ±0·68	26 (87%)	21 (70%) (7)‡	6 (20%)	18 (60%)	21 (70%)	15 (50%)	12 (40%)	19 (63%)	25 (83%)	5 (17%)

* One had silent neuritis initially, with overt neuritis later in lactation. One had overt neuritis initially, with silent neuritis later in lactation. †One had overt neuritis during pregnancy and silent neuritis during lactation. ‡Increased activity of leprosy as a transient phenomenon.

Table 3. Symptoms and clinical features in mothers who did not have erythema nodosum leprosum in pregnancy and lactation

Classif-ication	No. of women	Total duration of treatment (years) (Mean ±SEM)	Duration of effective treatment (years) (Mean ±SEM)	No. BI+ve	Increased activity of leprosy	Reversal reaction in skin (including histological up-and-down grading)	Enlarged nerves	Neuritis			Lymphad-enopathy	Complaint	
								Total No.	Overt	Silent		'Rheumatism'	Paraesthesiae
BL	35	6·53 ±0·82	6·33 ±0·83	30 (86%)	15 (43%) (2)†	8 (23%)	13 (37%)	13* (37%)	7 (20%)	8 (23%)	13 (37%)	14 (40%)	4 (11%)
LL	14	7·25 ±1·08	6·54 ±0·85	9 (64%)	8 (57%) (4)‡	0	3 (21%)	2 (14%)	1 (7%)	1 (7%)	2 (14%)	1 (7%)	0
Total	49	6·7 ±0·66	6·39 ±0·63	39 (80%)	23 (47%) (6)†	8 (16%)	16 (33%)	15 (31%)	8 (16%)	9 (18%)	15 (31%)	15 (31%)	4 (8%)

* One had overt neuritis with late silent neuritis, a second had silent neuritis with late overt neuritis. † Transient increase in activity, in one case there was late relapse during lactation. ‡ Transient increase in activity.

were more commonly seen in patients who also had ENL than those who did not have ENL, especially in the LL patients. Thus there appears to be a correlation between ENL, relapse, new nerve enlargement, neuritis and lymphadenopathy. The complaint of 'rheumatism' was heard from 90% of BL patients with ENL and 80% of LL patients with ENL. Paraesthesiae, 'burning sensation in the skin', was a complaint of pregnancy while 'rheumatism' tended to be a complaint of lactation. In the BL group, enlarged nerves, neuritis and lymphadenopathy were also associated with reversal reaction during lactation and followed relapse in late pregnancy.

ENL AND NEURITIS IN PREGNANCY AND LACTATION

The extent of nerve involvement in ENL in pregnancy and lactation has been shown in Figure 3. The degree of nerve damage is shown in Table 1. Six patients had 8 episodes of ENL nerve involvement with acutely tender peripheral nerves in which no motor or sensory loss was demonstrated. However, there were 30 episodes in which significant motor and/or sensory loss occurred. There was only one episode in which there was loss of function of a single nerve; however, the patient developed multi-nerve involvement during the next episode of neuritis.

We observed that many nerves were involved in each episode of neuritis. Usually in overt neuritis twice the number of nerves were recorded as showing tender nerve enlargement, as showed loss of function. This may reflect the fact that the methods of sensory testing were designed to demonstrate loss or recovery of protective sensation rather than absolute loss of sensation. Severe motor nerve damage was recorded in 13 episodes of neuritis and severe sensory nerve damage was recorded in 9 episodes of neuritis.

A further measurement of the severity of the neuritis is seen in the number of patients who required treatment with prednisolone for nerve damage for periods of up to several months. Six out of 8 BL patients and 10 out of 13 LL patients received prednisolone; 5 out of 16 patients receiving prednisolone and 1 of the 5 without prednisolone showed improvement in nerve function at the time of the last assessment.

ENL AND INFECTIONS SEEN DURING PREGNANCY AND LACTATION

Two patients, both LL, deserve special comment.

(i) S.M. A9/256, a secundigravida who had been treated with dapsone 100 mg daily for 3 years, was referred to the hospital during the second trimestre from an outlying clinic for severe ENL which had started during the first trimestre. During the first 6 months of pregnancy, she had severe ENL in the skin which required treatment with prednisolone 20–30 mg daily. In the third trimestre, she had a transient rise in BI, skin ENL persisted, and in addition she developed neuritis and arthritis with acutely tender swollen knees and hands. After delivery, the

ENL stopped suddenly, but restarted as abruptly 21 days postpartum, with skin, nerve and bone involvement, acutely tender tibiae and dactylitis. Chest X-ray showed pulmonary tuberculosis. She improved on treatment with anti-tuberculous drugs, and clofazimine for ENL and was discharged home for further treatment by her home clinic.

(ii) Y.T. A9/64, a gravida 4 who had received dapsone monotherapy for 9 years, had no problems during her pregnancy. At 6 months postpartum she was acutely ill with endemic typhus and required in-patient treatment for 3 weeks. During the first week of the febrile illness she had developed skin ENL. This became very troublesome and after 2 months ENL involved nerves and bone as well. Like S.M., she had acutely tender tibiae and dactylitis. At this time biopsy showed ENL in the skin and short solid AFB in deep muscle, indicating incipient relapse. She developed new nerve damage with motor and sensory loss. Despite treatment with prednisolone 20–30 mg daily, she had persistent sensory loss at her last assessment.

Discussion

It has been generally accepted that lepromatous patients who develop ENL do so within the first 2 years of treatment. An overall rate of approximately 40% has been recorded, of which 90% of LL (LL_p), 62% of LI (LL_s) and 32% of BL patients suffer from the reaction within $2\frac{1}{2}$ years of starting treatment.[9] It has been suggested that late ENL may be the first indication of the development of dapsone resistance, but studies in Ethiopia failed to confirm this.[22] Release of antigen during initial therapy, together with immunoglobulin and complement has been thought to form the immune complexes which have been considered as causative of most cases of ENL.[1–3] Pregnancy has been reported as precipitating ENL and relapse without comment on mechanism.[15–17, 23, 24]

During normal pregnancy there is an increase in the number of antibody–antigen complexes, particularly towards the end of pregnancy,[11, 12, 25] but the implications of this observation remain obscure. In studying patients with leprosy, it is tempting to link this general observation with the increased incidence of ENL observed in our study and assume a cause-and-effect association. However, this would not explain the initial peak of ENL in the first trimestre. During the first trimestre of pregnancy there is inversion of the T-cell: B-cell ratio due to physiological depletion of suppressor T-cells.[10] The hypothesis that the initial phase of ENL is due to imbalance of T-cell subsets with decrease in the population of suppressor T-cells[7] presents an interesting alternative which might well account for the upsurge of ENL seen in the first trimestre. Further evidence for the implication of disturbed T-cell function in the pathogenesis of ENL may be seen in the 'clinically puzzling mixtures of type 1 and type 2 reaction' observed in some of our patients associated with relapse.[21]

In 11 out of 21 cases, ENL preceded or accompanied the first sign of relapse.

Mouse foot-pad tests were undertaken in 7 of the 21 patients and all showed low-grade dapsone resistance.[19] This may indicate either that the patients had been taking their (self-administered) treatment irregularly: urine tests for dapsone were not performed to study the question; or that pregnancy immunosuppression is a factor in the stepwise development of dapsone resistance. It seems possible that in pregnancy, where there is a state of immunological instability, ENL is a significant symptom in, or sign of, the development of dapsone resistance.

Probably the most important observation in this study is the association between ENL and severe nerve damage. It is sometimes stated that although ENL can occur in nerves, causing severe nerve tenderness, major nerve damage does not usually occur. For this reason, treatment with corticosteroids is frequently eschewed and most patients are treated symptomatically. While this may be true of non-pregnant patients, the same cannot be said of women during pregnancy or lactation. We have already recorded an increased prevalence of neuritis in association with pregnancy and lactation.[21] It may be that with alterations of CMI during pregnancy and lactation, nerves previously considered as privileged sites for *M. leprae* become especially vulnerable.

The observation that ENL is more common in the skin during pregnancy and more common in nerve during lactation may be of interest in reappraising the pathogenesis of ENL. A similar observation has been made regarding the timing of reversal reaction in association with pregnancy and lactation.[26] It is tempting to suggest that, as in reversal reaction where surface antigens of *M. leprae* play a part in skin reactions while cytoplasmic antigens are responsible for reactions in nerve,[27] in ENL skin reaction occurs during the period of relapse when surface antigens are predominant and nerve reaction is seen as cytoplasmic antigens are exposed. Or, if, as has been suggested, CMI plays a part in the pathogenesis of ENL, a further explanation for the occurrence of ENL in the skin during pregnancy and in nerve during lactation could be as follows. During pregnancy, due to suppression of CMI, immune responses are weaker, hence antigen in nerves is less accessible and remains 'hidden' until postpartum when reactions are observed in nerve. Reaction in skin, due to the antigen being more accessible, can occur during pregnancy even though the immune response is diminished (D S Ridley, personal communication).

Evaluation of lymphocyte transformation (LTT) in pregnant women who were classified as cured tuberculoid (BT/RFC) increased our understanding of some of the hitherto 'bizarre' results observed in some women with borderline leprosy in reversal reaction (G Bjune, personal communication). In similar fashion, a prospective study of a few well-controlled lepromatous patients (LL_p, LL_s and BL) with ENL in early pregnancy—including measurement of total white cell count, T- and B-cells and lymphocyte transformation—might throw light on the pathogenesis of ENL in terms of T- and B-cell function and response to surface or cytoplasmic *M. leprae* antigen.

We have observed during the course of the study the coincidence of ENL and reversal reaction in patients who relapsed during late pregnancy and the puerperium. It is possible that some of the cases of late silent neuritis seen in lepromatous patients with ENL were actually due to reversal reaction rather than to ENL. A further study with serial nerve biopsies during pregnancy and lactation would be necessary to provide factual information on this point.

The role of infections other than leprosy in triggering off ENL is seen in two patients reported in detail. Persistent ENL has been associated with underlying tuberculosis (Pearson, unpublished observations), only remitting after treatment for tuberculosis was established. As both tuberculosis and endemic typhus are controlled to a variable extent by cell-mediated immunity, it is possible that T-cell suppression associated with those infections causes ENL, thus providing further supportive evidence for Mshana's hypothesis.

The significance of ENL in association with pregnancy and lactation is: (i) first occurrence in early pregnancy when the woman may not even realize that she is pregnant, especially if she is still lactating after her previous pregnancy; (ii) significant morbidity during pregnancy and lactation, possibly necessitating hospital treatment as an in-patient; (iii) association with relapse/dapsone resistance; (iv) a potential cause of permanent nerve damage; and (v) necessity for additional drug therapy.

In ideal circumstances, unexplained ENL occurring in a woman treated with anti-leprosy drugs for more than 4 years should alert the leprologist to carry out a urinary pregnancy test, a urinary examination for levels of dapsone, initial assessment for early dapsone resistance, and assessment of motor and sensory nerve function.

All drugs given during the first trimestre of pregnancy carry the risk of harming the foetus. Because of the teratotoxicity of thalidomide, it is absolutely contra-indicated in all women of child-bearing age. Prednisolone given during the first trimestre carries a slight risk of causing cleft palate. We have suggested that the best drug currently available would be clofazimine which, given from the second trimestre onwards for a period of approximately 1 year, would: (a) deal with the problems of transient relapse; and (b) prevent or treat ENL.[19]

However, clofazimine has not been used extensively during pregnancy and all cases so treated should be carefully documented and reported. In rat pregnancy, clofazimine has been shown to cause abortion,[28] and in human pregnancy there is suggestive evidence that clofazimine suppresses the placental production of oestriol, although the significance of this is not clear.[29]

Acknowledgments

We are most grateful to the staff and patients of the Addis Ababa Leprosy Hospital for their cooperation in this study; Miss Jean Watson, Mr Wim

Brandsma and the staff of the Physiotherapy Department for carrying out the sensory skin testing and voluntary muscle testing; and Dr B Naafs for measuring nerve conduction velocity in selected patients. We also thank Dr D S Ridley who provided independent histological classification of the patients in the study and who read the serial biopsies of patients in reaction.

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Lepr Rev (1984) **55,** 143–147

Short-course multi-drug therapy for paucibacillary patients in Guyana: preliminary communication

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Accepted for publication 19 September 1983

As from 1 December 1981 the WHO short-course multidrug regimen[1] was introduced into the Guyana Hansen's Disease Control Programme. It is too early yet to review results of treatment of multibacillary patients but this preliminary report describes the progress of 303 paucibacillary patients who had completed treatment by 31 May 1983.

Previous management of paucibacillary patients

Prior to December 1981, paucibacillary patients were treated with dapsone monotherapy (100 mg daily) until clinically inactive and, thereafter, maintained on dapsone at full dosage for periods ranging from 2 years for TT to 5 years for BT patients. About 30 patients were released from treatment annually until 1981 when 64 patients were released from control. Relapses were not seen. Patients attended the clinic monthly at first and subsequently every 2–3 months.

New treatment regimen

All patients moved on to the new regimen at their next, routine clinic appointment after 1 December 1981 so that by the end of February 1982 most of the paucibacillary patients remaining in touch were on a regimen consisting of a single, monthly dose of rifampicin 600 mg plus dapsone 100 mg given under supervision at clinic, together with a daily dose of dapsone 100 mg to be taken at home. Although not specifically advised in the WHO study, it has been found important, for psychological reasons, that a dapsone tablet is given under supervision along with the rifampicin at the monthly clinic. Otherwise there is a

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danger that both patients and staff will underestimate the value of dapsone and conclude that because of the emphasis given to them, only the coloured capsules are essential for cure.

Evaluation

In evaluating this field trial of a new treatment regimen the following points were considered: Is the treatment acceptable to patients? Is the treatment acceptable to and manageable by the nursing staff? Are results comparable with those previously obtained? Are there unacceptable side-effects or unacceptable reactions?

Patient appeal

Patients definitely prefer the new regimen. Much time was spent explaining it to each patient and their very positive response is reflected in the small number of missed appointments—only 8% having to extend their treatment period over a seventh month because of a missed, single dose of rifampicin (a further 4% missed more than one appointment). It had been anticipated that the biggest problem would be the provision of support for patients anxious to continue treatment because of the presence of incompletely resolved lesions. However, this did not prove as big a problem as had been anticipated. Extra time was spent in counselling these patients and they were assured that they could attend clinic whenever they wanted to. The only patient who needed further support was a young man who became inappropriately worried over a few, faint stains sometime after his very obvious facial BT lesions had faded. It subsequently transpired that he was planning to emigrate.

Acceptable by nursing staff

The necessity for all patients to attend clinic monthly produced a rise of 120% in the number of patients seen at clinic in 1982. This tremendous increase in workload was cheerfully accepted by the clinic nurses once they understood the reasons for the change. As we move through 1983/84, many multibacillary patients will come to the end of their treatment and we shall move onto surveillance with a reduction in the clinic workload.

Results

Patients can be grouped into those who were active at the start of the new

treatment and those who were already inactive but who had not yet completed the previously accepted norm of post-activity treatment. As expected, the latter remain inactive but will be under surveillance for a minimum of 2 years. Active patients can be divided into TT and BT groups, the former consisting of patients with either a single macule or a single enlarged nerve. These TT lesions have either cleared completely or continue to regress at a satisfactory rate. No relapses have been seen so far. Active BT lesions, as expected, have taken longer to resolve but most continue to improve steadily. Two patients have presented as relapses—both within 8 months of completing treatment. One is a women in her mid-seventies and the other a teenage girl who became pregnant and in whom there was certainly an inadequate drug intake. These figures give a relapse rate of 1% of 192 BT patients at risk.

Side-effects

Rifampicin is given as near to the monthly due date as possible so as to avoid the well-documented dangers of too closely spaced, intermittent rifampicin. In fact only one patient was adversely affected by this drug. A middle-aged woman (TT) experienced a typical cutaneous syndrome[2] with an irritating erythematous and oedematous rash developing over face, scalp and neck about 1 hour after rifampicin. She was given an oral antihistamine and the rash gradually subsided over the next hour. As this patient was inactive and already within a few months of completing the normal span of dapsone monotherapy she was removed from the project and completed her treatment on dapsone alone. Later in the year a young woman with multibacillary disease (this group will be reported in a later publication) experienced a similar rash—beginning with an intense irritation of the palms and developing into a maculo-papular rash of small urticarial-type weals distributed mainly over the upper half of the body and most thickly over the head and neck. As with the previous patient the rash settled with re-assurance and antihistamine alone. There is no doubt that these rashes must be attributed to rifampicin as they were identical in type, no other drugs were being taken and in the second patient the rash recurred on challenge with rifampicin alone. It has been possible to desensitize this patient[3] and she has continued her treatment without mishap.

Type I reaction

Three instances of Type I reaction[4] occurred in BT patients during the period under review. All three patients already had a moderately severe reaction on diagnosis—there were no instances of reaction occurring in patients who were reaction-free at diagnosis. The reactions were handled in a routine manner and

did not present any unusual difficulties. Clinical details of the first case are as follows (the other two patients are still undergoing treatment and will be described in a later publication). Reaction involving large skin lesions scattered over body recurred after changing to the new regimen but settled under prednisolone without nerve damage. The presenting reaction had fluctuated over the previous 9 months' treatment but was reasonably well controlled at the time of the change. Chemotherapy was continued throughout and for 6 months after withdrawal of prednisolone. There is nothing to indicate that the use of rifampicin contributed to the severity of this reaction. We have seen equally severe reactions developing with patients on dapsone monotherapy. In this respect it is particularly interesting that no reaction occurred except in those patients who were already reacting on presentation and, so far, no reaction has been seen in any patient after completion of treatment.

Patients taking alternative therapy

During the 18 months under review there were three patients who failed to complete the recommended monotherapy. (i) The middle-aged woman with a cutaneous syndrome reaction to rifampicin (see above), who completed her treatment on dapsone monotherapy. (ii) A teenaged boy with an indeterminate facial lesion who developed infectious mononucleosis (not a dapsone drug reaction) after 6 months on dapsone monotherapy. On recovery he refused dapsone but agreed to take thiambutosine. When the programme changed to dapsone and intermittent rifampicin this patient received thiambutosine and intermittent rifampicin, as he remained unwilling to take dapsone. (iii) A young woman with very early BT lesions developed an extensive, irritating papular rash 2 weeks after starting treatment. The rash settled with corticosteroid ointment and an oral antihistamine but recurred with her second month's treatment, accompanied by facial oedema which required prednisolone for control. Challenge with rifampicin alone was uneventful but challenge with dapsone produced severe facial oedema. Daily dapsone was, therefore, replaced by daily clofazimine 50 mg but the patient subsequently refused this on the grounds of 'skin irritation'. Challenge did not support this complaint but as the patient had had a very uncomfortable experience it was thought wiser to maintain her on monthly, supervised drugs only—rifampicin 600 mg together with clofazimine 300 mg.[5] No further adverse effects were noted and the patient was on the verge of inactivity on completing treatment.

Discussion

Two hundred and forty-six of the 303 patients under review completed treatment

during 1982 and 57 during the first 5 months of 1983. It is certainly too soon for a comprehensive review of results but on the evidence available so far the WHO recommendations for paucibacillary patients are effective. There have been neither relapses nor reactions among three indeterminate (I) and 108 TT patients at risk and a relapse rate of 1% amongst the 192 BT patients is acceptable. However, these 192 patients include many who had already had some previous treatment and it is possible that the relapse rate may rise in the future when all patients are 'new' patients.

The crucial factor here is surely time. The earlier the treatment is given the lower the incidence of reactions, nerve damage and relapse—and conversely, the longer treatment is delayed the more likelihood there is of complications. The identification of early cases is, therefore, a matter of the highest priority. The introduction of a short-term treatment regimen for paucibacillary patients has reduced our gross caseload in Guyana to below 60% of its previous level. This gives us valuable time in which to expand and to concentrate on health education and contact tracing in a determined effort to reach more patients and to treat them earlier in the course of their illness. Experience so far suggests that there is no need to fear that patients released from treatment will not report back on deteriorating; on the contrary, patients frequently return for treatment of incidental skin complaints and for reassurance where macules, though fading, are still present. Perhaps one of the most important benefits to be expected from the new regimen is that the release of large numbers of satisfied patients, after such a relatively short period of treatment, will have a tremendously beneficial impact on case finding. A further account of progress in the treatment of paucibacillary, and also multibacillary cases, will be published later.

Acknowledgments

This project received aid from the American Leprosy Missions Inc., Pan-American Health Organisation, LEPRA, and the Netherlands Leprosy Relief Association.

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Lepr Rev (1984) **55,** 149–157

Dapsone-resistant leprosy in Addis Ababa: a progress report

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Accepted for publication 5 October 1983

Summary Two hundred and twelve lepromatous patients, presenting with suspected dapsone-resistant leprosy in the 5-year period 1973–77, were taken into trial treatment with dapsone. Clinically, 55% have been proven to be dapsone resistant and the remainder are continuing to respond to full dosage dapsone after 4·5 to 9 years.

This clinical observation contrasts with results of the dapsone-sensitivity studies in mice which demonstrated in 86% of the 43 patients examined dapsone-resistant bacilli. The relevance of partial dapsone resistance, diagnosed in mouse foot-pad tests, is challenged and a modified definition of dapsone resistance is suggested. The annual incidence of proven dapsone-resistant leprosy over the period 1973–77 was 1·8%, resulting in a prevalence in 1978 of 119 per 1000 lepromatous cases on register in Addis Ababa.

Introduction

In 1973 the Leprosy Unit of the National Institute for Medical Research in London initiated a Medical Research Council (MRC) Project in the charge of Dr John Pearson at the All Africa Leprosy Rehabilitation and Training Centre (ALERT). All leprosy patients in the Addis Ababa area are started on treatment at this centre and their condition is reviewed, at least half-yearly, at one of its out-patient clinics. All cases with clinical suspicion of dapsone-resistant leprosy were referred to a special clinic for assessment and follow-up, conducted by the MRC. After closure of this project in 1978, the clinic continued its activities with staff of ALERT Hospital until the end of 1982, when it was felt that this special clinic was no longer needed, and its operation discontinued.

The MRC studies, carried out from 1973 to 1978, revealed a higher incidence

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and prevalence of dapsone resistance than has been reported elsewhere. The incidence of suspected dapsone resistance was about 3% per year and the minimum prevalence of dapsone resistance was found to be 100 per 1000 lepromatous patients in 1978. On the assumption that the majority of relapsed lepromatous cases, despite initial improvement on trial treatment with full dosage of dapsone, would later prove to be resistant, the probable prevalence of dapsone resistance in 1978 was estimated to be 190 per 1000 registered lepromatous cases.[1–4]

Indeed, if all suspected cases would prove to be dapsone resistant, it would ensure, if continued unchecked, that about 30% of the patients with lepromatous leprosy in the Addis Ababa area would develop dapsone resistance by 1980.[1] In such a situation the efficacy of dapsone, even in combinations of drugs, would become doubtful. In 1974, however, the treatment policy was changed. The low-dosage schedule of dapsone and discontinuation of dapsone during reactions, introduced 10 years earlier, was abandoned. In spite of the generally low treatment compliance of the Addis Ababa patients, this change of treatment policy might well have had a significant influence on the rate of emergence of dapsone-resistant strains.

Therefore, in 1982, we reviewed the clinical and bacteriological condition of those patients who were suspected of suffering from dapsone-resistant leprosy in the period 1973–77 and were still on trial treatment with a full dose of dapsone. Relevant information on trial patients who changed treatment because of clinical deterioration was obtained from their case notes.

This study has been undertaken primarily to estimate more accurately, with hindsight, the prevalence of dapsone-resistant leprosy in 1978 and the annual incidence in the period 1973–77. An attempt has also been made to study the relationship between the outcome of trial treatment and the results of mouse food-pad tests in the trial patients.

Patients and methods

Details of the selection of patients for this study, their clinical follow-up and treatment, selection for mouse foot-pad tests and the technique of the mouse studies have been reported.[3] Between 1973 and 1978, patients started on the trial treatment with full dosage of dapsone (100 mg daily or 375 mg weekly, by injection). Those who were doing well were in the following years continued on this regimen. Assessment, carried out 6 monthly, included clinical drawings and skin smears from the same sites selected at previous assessments, unless new active lesions had appeared. Biopsies for histopathological examination were repeated if the clinical condition had deteriorated. The period of trial treatment was terminated when the patient's condition failed to improve or was aggravated and, therefore, suggested dapsone-resistant leprosy.

During the period 1973–77 the total intake of relapsed and, therefore, suspected dapsone-resistant lepromatous patients had been 260 out of the 1500 lepromatous cases registered in the Addis Ababa area. About 87% of these patients presented with a 'classical history' of deterioration despite regular treatment. The remaining 13% were suspected because of slow improvement, reactions occurring later than usual, a solitary leproma of the eye or a relapse after discontinuation of treatment (group with 'atypical presentation'). By the end of 1977 the percentage of proven dapsone resistance was about equal in both groups. This observation seems to make it unnecessary to maintain the distinction between these two groups.

In 48 out of the total number of 260 patients, treatment with dapsone was discontinued at once because of advanced disease, social reasons or severe complications. Mouse foot-pad (MFP) tests, carried out in 25 (52%), had confirmed dapsone resistance in 24 cases. The remaining 212 patients continued to take dapsone in full dosage, supervised as much as possible. The great majority attended the hospital regularly for treatment and follow-up: only 6 patients (3%) have been lost (3 each by default and known death).

Another 6 cases were removed from the trial because of mouse foot-pad proven dapsone sensitivity (3) or because they developed severe neuritis requiring change to clofazimine treatment. When the trial was reviewed in 1982, patients had been studied for a minimum of 4·5 years and a maximum of 9 years.

Results

The results of the review of the 212 patients are presented in Tables 1 and 2. It appears from Table 2 that the majority of the trial cases which proved to be suffering from progressive and, therefore, dapsone-resistant leprosy, did so in the first 3 years of the trial treatment. Thereafter, the probability was around 5% per year, decreasing to zero after more than 6 years of trial treatment. Forty-five percent of the patients responded to dapsone throughout the trial period.

This prolonged response to dapsone treatment contrasted with the results of the dapsone-sensitivity tests in mice performed in 43 (20%) of the 212 trial patients (see Table 3). In 23 patients the MFP test was carried out at the start of the trial, in 20 at the end. Only 5 (22%) of the *Mycobacterium leprae* strains tested at the start, and 6 (14%) of the total number tested, were found to be fully sensitive.

Table 4 presents the relationship between the outcome of trial treatment and the results of MFP tests for those patients tested at the start of the trial. Interestingly, seven resistant strains, including one fully resistant strain, are continuing to respond to a full dose of dapsone in the patients who are still being followed for between 5 and 9 years.

As can be seen from Table 1 the mean annual incidence of suspected and

Table 1. Number of patients with suspected dapsone-resistant leprosy during the period 1973–77 on a total of 1500 registered lepromatous cases

	Total no. of suspected cases	No. of cases changing treatment at once	Total	No. of cases taken into trial deteriorated clinically before 1978 or 1978–82		Total no. of patients with dapsone-resistant leprosy (1973–77)*
	(1)+(2)	(1)	(2)	(3)	(4)	(1)+(3)
1973	46	21	25	13	0	34
1974	56	12	44	23	3	35
1975	47	1	46	20	4	21
1976	62	5	57	23	6	28
1977	49	9	40	11	9	20
Total	260†	48	212	90	22	138‡

* Total number of patients with proven dapsone-resistance on the assumption that all patients who changed treatment at once or deteriorated on supervised full dose were indeed dapsone-resistant.

† Mean annual incidence of suspected dapsone-resistant leprosy 1973–77—3·5%.

‡ Mean annual incidence of proven dapsone-resistant leprosy 1973–77—1·8%.

Table 2. Time table of occurrence of dapsone-resistant leprosy in lepromatous patients presenting with a relapse during 1973–77

T_x		N_x	R_x	W_x		Q_x	P_x	L_x
1		212	42	3	42/210·5=	0·200	0·800	80·0
2		167	30	3	30/165·5=	0·181	0·819	65·5
3		134	25	1	25/133·5=	0·187	0·813	53·3
4		108	7	3	7/106·5=	0·066	0·934	49·8
5		98	5	1	5/97·5=	0·051	0·949	47·2
6	92−17=	75	3	0	3/75=	0·040	0·960	45·3
7	72−24=	48	0	0		0·000	1·000	45·3
8	48−21=	27	0	1		0·000	1·000	45·3
9	26−16=	10	0	0		0·000	1·000	45·3

T_x = Years since start of trial treatment.

N_x = Number of relapsed patients on trial treatment at T_x.

R_x = Number of patients with clinically proven dapsone-resistant leprosy.

W_x = Number of patients lost from trial (total of 12).

Q_x = Probability of showing clinically dapsone-resistant leprosy in a 1-year period.

P_x = Probability of remaining in trial treatment without clinical deterioration during 1 year.

L_x = Percentage remaining in trial treatment for x years.

Table 3. Results of mouse foot-pad tests for dapsone sensitivity in 260 patients with suspected dapsone-resistant leprosy

Degree of sensitivity		Patients tested at start of trial	Patients tested when deteriorating on trial treatment	'No trial' patients
Sensitive		5	1	1
Not fully titrated*		4	10	11
Resist 0·0001%		5	0	6
Resist 0·001%		5	3	0
Resist 0·01%		4	6	7
	Total tested	$\frac{23}{212} = 11\%$	$\frac{20}{112} = 18\%$	$\frac{25}{48} = 52\%$

* See legends, Table 4.

Table 4. Results of mouse foot-pad tests carried out in 23 patients at the start of trial treatment and the outcome of trial treatment

	No. tested	Sensitive strains	Total no. of resistant strains	Degree of sensitivity			
				Nft	L	I	F
Clinically resistant	12	1	11	2	3	3	3
Responding to dapsone	11	4	7	2	2	2	1

Nft: 'Not fully titrated': not screened against dapsone 0·01% but found resistant to one of the lower dapsone concentrations.

L: 'Low-grade resistant': multiplying in mice on dapsone 0·0001% but not on higher dapsone concentrations.

I: 'Intermediate resistant': multiplying in mice on dapsone 0·001% but not on a higher dapsone concentration.

F: 'Fully resistant': multiplying in mice on dapsone 0·01%.

proven dapsone-resistant leprosy in the period 1973–77 was, respectively, 3·5 and 1·8%.

The mean duration of treatment with dapsone prior to the relapse in those who proved to be dapsone-resistant was 9·5 years and did not differ from that of the patients in whom the dapsone treatment could be continued.

Discussion

The following conclusions can be drawn from this study:

(a) Forty-seven percent of the patients presenting with suspected dapsone-resistance and started on trial treatment with full dosage dapsone, proved clinically to be suffering from dapsone-resistant leprosy within the first 3 years of trial treatment. In the following 3 years an additional 8% stopped responding satisfactorily (Table 2).

(b) The remaining 45% of the patients continued to respond well to full dosage dapsone for a minimum of 5 years. The initial relapse in these patients was, therefore, apparently caused by a failure of self-medication with dapsone. One should keep this in mind when selecting an alternative regimen for relapsed cases, particularly if this includes rifampicin: the medication should be sufficiently supervised to prevent the emergence of rifampicin-resistant *M. leprae*.

(c) The annual incidence over the period 1973–77 of proven dapsone-resistant leprosy was 1·8% (Table 1). This rate is not representative for Ethiopia, because in

the past great numbers of leprosy patients with social or medical problems moved from the rural areas into Addis Ababa in search of a living or 'better treatment' and this group might, therefore, be quite different as regards duration and regularity of drug intake, frequency of complications, etc., compared to the patients attending a rural clinic.

(d) By the end of 1972, 41 patients were already clinically diagnosed as suffering from dapsone-resistant leprosy.[2] These, added to the 138 patients discovered between 1973 and 1977, give a known prevalence on 1 January 1978 of 119 per 1000 registered lepromatous cases, which is close to the previously estimated minimum prevalence of 100 per 1000 for that year.[4]

(e) The clinical observations were, to a large extent, in contrast with the results of the MFP tests which were carried out in 43 of the 212 suspected dapsone-resistant patients and which in 86% demonstrated dapsone resistance (Table 3).

This high percentage, as compared with 55% clinical dapsone resistance, is not explained by the fact that 20 of the 43 tests were carried out at the end of the trial period, when dapsone resistance was already clinically demonstrated. A comparable figure of 78% was found in the 23 patients in whom the study was done at the intake in the trial. In this group of patients no evidence was shown of a relation between the outcome of trial treatment and the results of the MFP tests (see Table 4). On the contrary, seven of the foot-pad proven dapsone-resistant patients continued to respond to full-dosage dapsone for more than 5 years. They are still bacteriologically negative and clinically quiescent at this time.

The discrepancy between the clinical and laboratory findings may to some extent be explained by the difference in the method used to diagnose dapsone-resistant leprosy. Strains of *M. leprae* capable of multiplying in mice to which dapsone has been administered in a concentration of 0·1 mg per 100 g of food (0·0001% in diet), but inhibited by a ten-fold higher concentration, are defined as partially or low-grade resistant.

But a 100-fold higher concentration achieves in mice a dapsone concentration roughly equal to that found in plasma of patients administered 100 mg dapsone daily. A strain found to be partially resistant in the laboratory will, therefore, in man still be inhibited by the now generally accepted daily dosage of 100 mg dapsone and apparently may continue to do so for many years (see Table 2). This strain appears thus, on clinical grounds, to be susceptible to dapsone. It seems, therefore, that the laboratory diagnosis of partial dapsone resistance, which had clinical implications in the era of the low-dosage schedule of dapsone, has lost a great deal of its importance.

The concentration of 10 mg dapsone per 100 g diet has in the 1960's been considered[5, 6] the demarcation level for testing dapsone resistance: all strains of *M. leprae* multiplying in mice fed 0·03% or more in their diet were considered dapsone resistant. The assertion in later publications,[2, 3, 6, 7] that patients harbouring bacilli which multiply in mice fed 0·0001 or 0·001% dapsone in the

diet would respond for only a few more years to dapsone in full dosage has, to our knowledge, not been supported by hard facts. On the contrary, satisfactory response to dapsone monotherapy for up to 10 years in 11 out of 12 patients with foot-pad evidence of mainly low-grade primary dapsone-resistant leprosy has been reported.[8, 9]

Current textbooks of microbiology dealing with the interpretation of susceptibility tests in other bacterial diseases take into account the clinical experience with the treatment of the particular type of infection involved. A strain of micro-organisms is defined as resistant to a chemotherapeutic agent, if the strain tested is not completely inhibited by the concentration reached at the site of infection with a dosage within the usual therapeutic range.[10, 11] This contrasts with the accepted definition of dapsone resistance in *M. leprae*, which only takes into account the MIC as estimated in mouse studies. Leprosy is then defined as dapsone resistant when the causal bacilli multiply in mice receiving 0·0001% dapsone in the diet, a dosage comparable with an intake of 1 mg dapsone daily in man.[2, 12–14] This definition ought to be revised as it has, at the present time, no clinical relevance and is confusing if used interchangeably with the clinical definition of dapsone resistance on which the majority of leprosy programmes have to rely. We, therefore, suggest that only strains multiplying in patients on full dosage dapsone or in mice fed 0·01% dapsone in the diet, are considered dapsone resistant.

(f) One particular strain of *M. leprae*, multiplying at a dapsone concentration of 0·01%, was obtained from a patient who thereafter responded to dapsone monotherapy for a minimum of 9 years. This might be explained by the presence of a small proportion of fully dapsone-resistant bacilli which multiplied in mice but were possibly killed in the patient by factors other than chemotherapy. In such cases one would expect multiplication in only a proportion of the mice treated with the dapsone 0·01% diet, but particulars of the test are not available. Repeated histological examinations of the patient showed an upgrading reaction.

(g) The duration of dapsone monotherapy in itself does not seem an important determining factor in the emergence of dapsone-resistant strains, because the duration of treatment prior to the relapse was equal in the group of trial patients who proved to be dapsone resistant and the group who continued to respond well to dapsone.

Acknowledgments

We gratefully acknowledge the major contribution of the MRC Staff at ALERT, in particular Dr J M H Pearson, who designed and initiated this study, carried out most of the mouse foot-pad studies and followed the patients until August 1978. We thank our colleagues at ALERT for their kind cooperation, the registration staff for their patience, and the Armauer Hansen Research Institute for the accommodation of the experimental mice.

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Urban leprosy—an appraisal from northern India

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Accepted for publication 6 September 1983

Summary From an urban leprosy programme in India details were collected from 1661 new patients in order to delineate its pattern clearly. It was revealed from this study that males aged from 20 to 29 years were the largest and commonest age-at-onset group, though no age group was immune to leprosy. The patients were largely derived from unskilled workers and belonged to the low-income strata. Urban leprosy as such appears to be a negligible problem but a threatening situation is developing because of the influx of migrants from endemic belts, a pattern seen in almost all studies of this kind. This study also draws attention to the high percentage of lepromatous or borderline-lepromatous registered in an urban situation.

Introduction

The epidemiological features of leprosy are well known in the endemic areas. However, very little attention has been paid to the problem of leprosy in the northern parts of India, largely recognized as low-endemic areas. Furthermore, it is interesting to note the pattern of the disease in urban leprosy centres which register patients not only from that area but also from adjoining states. We report our assessment of the problem of urban leprosy in the northern parts of the Indian subcontinent.

Material and methods

In all, 1661 new leprosy patients, attending the urban leprosy centre for over a

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0305-7518/84/0550159+08 $01.00

period of 6 years ending March 1983, formed the subject matter for the study. The bulk of the patients were either referred to us for exclusion of leprosy, or were detected while being examined for another medical problem. Only a few reported to us with suggestive symptoms of leprosy, such as an apparent change in skin colour, numbness and tingling, recurrent inadvertent trauma or burns, bleeding or drying of the nose and alteration in facial appearance. Occasionally, redness and swelling of the skin lesions and/or fever and pain in the joints were the presenting features. Deformities of varying grades were also an indication of leprosy and are the subject of a separate paper. In each case a thorough investigation of the probable evolution of the disease was done and recorded in a protocol. In particular, emphasis was laid on the place of residence, occupation, income, age, sex and duration of disease. An age-at-onset was computed by subtracting the duration of the disease from that of the age at the time of reporting. This was difficult to ascertain since very few patients could account precisely for the onset of leprosy because of its innocuous initial clinical presentation. Nevertheless, complemented recall method was relied upon for finding out approximate age-at-onset. The patients were subjected to a set of procedures including the recording of morphological features, bacterial index, lepromin test and histopathological examination to identify their position on the leprosy spectrum.

Observations

AGE

All the age groups were affected by the disease. The number, however, was fairly sizeable in the age groups 20–29 and 30–39 years. Only 16 patients had contracted the disease before 9 years of age. Details of other age groups are given in Table 1.

AGE-AT-ONSET

The majority (36·06%) of patients had the onset of the disease between 20 and 29 years. Only 2·58% of the cases had the onset before 9 years of age. This is depicted in Table 2. There was no statistically significant relation between age-at-onset and sex ($\chi^2 = 10{\cdot}19$, df $= 6$, $P > 0{\cdot}05$).

SEX

There were 1353 males and 308 females. The ratio being 4·3:1.

Table 1. Age distribution according to years

Age groups (years)	Year						Total	%
	1977	1978	1979	1980	1981	1982–83		
0–9	04	03	03	03	01	02	16	0·96
10–19	31	21	25	36	36	36	185	11·56
20–29	68	64	84	118	76	179	589	32·45
30–39	54	57	44	85	37	86	363	21·85
40–49	35	41	38	42	36	59	251	15·11
50–59	20	31	30	32	28	55	196	10·60
60–69	12	14	15	19	06	14	80	4·82
70+	06	04	05	07	08	04	34	2·05
Age not known	05	01	—	—	04	—	10	0·60
Total	235	236	244	342	232	435	1724	100·00

Table 2. Distribution of age-at-onset and sex

Age at onset (years)	Sex		Total
	Males	Females	
0–9	39	4	43
10–19	298	79	377
20–29	493	106	599
30–39	246	61	307
40–49	160	36	196
50–59	82	151	97
60–69	19	7	26
70+	16	0	16
Total	1353	308	1661

$\chi^6 = 10{\cdot}19$, df = 6, not significant ($P > 0{\cdot}05$)

PLACE OF RESIDENCE

Nine hundred and twenty-five patients had come from Uttar Pradesh, 314 from Bihar, 178 from Delhi, 33 from Haryana and 15 from Punjab, and the influx of these patients has been continuous. Place of residence according to the year of their applying for treatment is depicted in Table 3. Interestingly, a relatively large number of patients were diagnosed in the course of 1979–80.

Table 3. State distribution of leprosy

Year	States						
	U.P.	Bihar	Others	Delhi	Haryana	Punjab	Total
1977	133	19	37	34	08	04	235
1978	129	33	35	30	08	01	236
1979	148	37	29	25	03	02	244
1980	197	80	26	30	05	04	342
1981	123	50	27	27	02	03	232
1982–83	195	95	42	32	07	01	372
Total	925	314	196	178	33	15	1661

Table 4. Yearly income distribution of leprosy

Year	Monthly income (in rupees)						
	0–100	101–200	201–300	301–400	401–500	500 & above	Total
1977	57	113	40	18	3	4	235
1978	53	109	39	19	11	5	236
1979	62	101	48	11	8	4	244
1980	73	115	81	33	29	11	342
1981	39	91	65	18	9	10	232
1982–83	153	72	84	30	18	15	372
Total	437	601	357	129	78	49	1661

INCOME

The disease was largely seen to affect the lower income group (Table 4).

OCCUPATION

Unskilled workers, skilled workers, housewives, farmers and unemployed people were affected in that sequence.

LEPROSY GROUPS

The different groups of leprosy according to the year of reporting are shown in Table 5. It is evident, that the most common group was borderline (44·25%),

Table 5. Year distribution of leprosy groups

Year	Groups of leprosy										
	TT	I	BT		BB		BL		LL	N	Total
1977	65	5	27	—	26	4	32	7	52	17	235
1978	56	3	25	*8*	27	*9*	26	*11*	49	22	236
1979	69	16	21	*8*	26	*9*	21	*11*	52	15	244
1980	118	8	37	*9*	26	*12*	21	*20*	74	17	342
1981	50	4	42	*6*	25	*16*	19	*4*	51	15	232
1982–83	42	5	87	*8*	57	6	34	*7*	96	31	372
Total	400	40	239	40	187	56	153	60	369	117	1661

Table 6. Distribution of leprosy groups and age-at-onset

Age at onset (years)	Groups of leprosy					Total	%
	I	TT	Borderline	LL	N		
0–9	1	20	17	3	2	43	2·59
10–19	11	108	176	66	16	377	22·70
20–29	22	165	234	132	46	599	36·06
30–39	5	53	154	77	18	307	18·48
40–49	1	36	98	45	16	196	11·80
50–59	—	11	47	31	8	97	5·84
60+	—	6	3	9	8	26	1·57
Not known	—	1	6	6	3	16	0·96
Total	40	400	735	369	117	1661	100·00

$\chi^2 = 65{\cdot}507$, df = 16, highly significant $P < 0{\cdot}001$

followed by tuberculoid tuberculoid (24·08%), and lepromatous leprosy (22·22%). It is clear that borderline borderline and lepromatous leprosy—infectious—constituted 66·47% of the total cases. Neuritic and indeterminate leprosy formed only 7·04% and 2·41% of the total cases, respectively.

AGE-AT-ONSET AND LEPROSY GROUPS

The age-at-onset and different leprosy groups are depicted in Table 6. There was a statistically significant relationship between the age-at-onset and different leprosy groups ($\chi^2 = 65{\cdot}50$, df = 16, $P < 0{\cdot}001$).

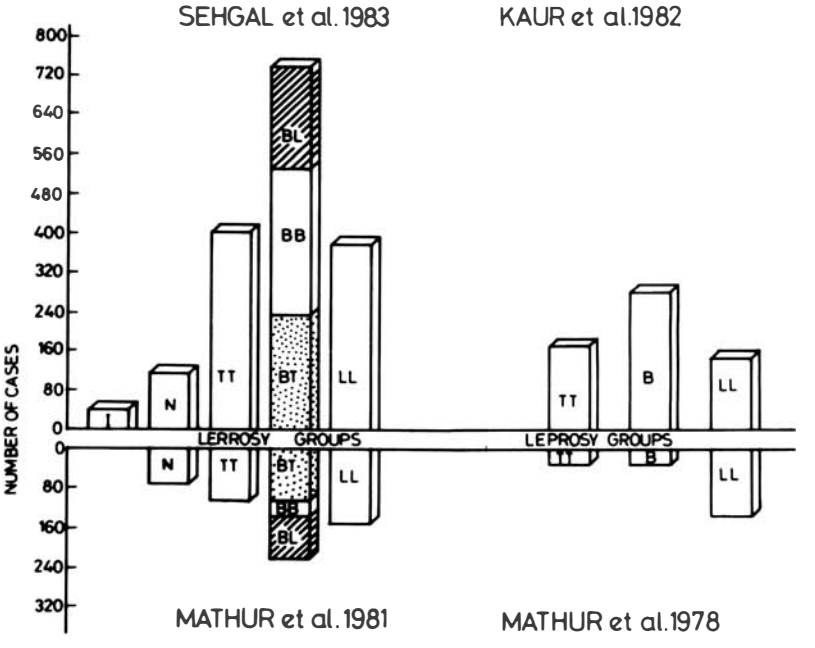

Figure 1. Comparison of leprosy groups in urban situations.

The comparative evaluation of our data with those reported earlier from Chandigarh, Jodhpur and Jaipur is shown in the accompanying diagram (Figure 1).

Discussion

Published data on the epidemiology of leprosy are primarily based on studies from large endemic areas and it was, therefore, considered interesting to find out the endemicity of leprosy in an urban situation.

The majority of our patients were males. This is a well-known finding in studies of this nature, as confirmed by several investigators.[1–8] It is difficult to account for this situation. Nonetheless, it may be because of several factors like industrialization, urbanization and more opportunities for contact in males. Social customs and taboos may account for the smaller number of females reporting for treatment to a hospital. Younger patients in the age group 20–29 years were found to suffer frequently. This is in keeping with our earlier reports[1,2,5] and those of other workers.[6–11] However, this observation is in contrast to that of earlier findings.[12–14] It is not possible to advance an adequate reason for this age distribution, though intimate skin-to-skin contact and a variable and long incubation period may be considered.

Table 7. Comparison of age-at-onset from India—percent in different age groups

Age (years)	Authors					
	Sehgal[1] Varanasi	Sehgal *et al*[2] Goa	Sehgal *et al*[5] New Delhi	Kaur *et al*[8] Chandigarh	Guha *et al*[11] Varanasi	Present study
0–9	3·5	5·3	2·94	2·0	6·2	2·59
10–19	16·1	14·5	18·88	12·4	20·0	22·70
20–29	27·9	29·1	30·43	32·8	27·0	36·06
30–39	24·3	22·9	21·43	19·7	23·0	18·48
40–49	15·4	12·1	14·87	15·6	10·7	11·80
50 and above	12·8	16·1	8·73	17·1	13·0	7·41

Our study indicates the commonest age-at-onset to be between 20 and 29 years. The comparison of this data with the studies conducted at other urban centres like Varanasi,[1, 11] Goa,[2, 3] Punjab,[10] Chandigarh[8] and Delhi[5] revealed almost identical findings (Table 7). Varma & Prasad[9] from Lucknow reported that the majority of cases had the onset between 10 and 29 years of age, while Ali[15] from Chingleput found it to be equally spread between 0 and 39 years.

The distribution of patients by state showed that the majority of patients were from Uttar Pradesh and Bihar, well known for their high endemicity. It appears from our study, that leprosy as such is a small problem in Delhi itself. Certainly, this being a capital city, there is an influx of large numbers of patients from neighbouring states, who not only come for specialist treatment, but also in search of work.

The majority of cases were from a low-income group. This is a common observation. Most of those with leprosy were unskilled workers, while students and service people were those least affected. Our views are shared by Kaur *et al.*[8]

The large number of leprosy patients in the infectious part of the leprosy spectrum was a startling feature of our study, but not in any way different from the studies conducted in urban centres.[6–8, 10] Several factors, namely migration of population, industrialization and urbanization may be blamed for the present situation. Similar views were expressed by Mathur *et al*,[6] who attributed the increase in leprosy patients in Jodhpur to increased migration of begging leprosy patients. In the opinion of Mani & Mathew,[10] the increase of leprosy in Punjab may be due to a floating population of migrant labourers from Bihar and Eastern U.P., which may constitute about 10% of the population of Punjab. However, in a study from Goa[3] where there was hardly any migrant population, almost half of the leprosy patients belonged to the tuberculoid group, thus reaffirming our impression outlined above.

Our study indicates that urban leprosy must be taken very seriously indeed in

India, not only because of its magnitude in the cities, but also because of its implications for the further development of the National Leprosy Eradication Programme.

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High density lipoprotein cholesterol (HDL-C) analysis in leprosy patients

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Accepted for publication 18 August 1983

Summary A study was undertaken with an aim to find out the levels of circulating high density lipoprotein (HDL) cholesterol and ratio of this fraction to total blood cholesterol in lepromatous leprosy patients before and after drug therapy. The healthy contacts of these patients were considered as control subjects of the study. The subjects were distributed in three groups on the basis of their age. HDL–cholesterol to total cholesterol ratio was significantly raised in both treated and untreated patients in all three groups compared to the healthy controls. The data may explain the low risk of myocardial infarction due to atherosclerosis in leprosy patients.

Introduction

A strong inverse relation exists between plasma levels of high density lipoprotein (HDL) and mortality from coronary heart disease. The role of HDL as a risk-preventing factor and the importance of this cholesterol-carrying protein in patients who are likely to develop risk of coronary heart disease have been of great importance to both clinicians and biochemists. High levels of serum HDL–C are associated with a low incidence of the complications of atherosclerosis, whereas low levels are associated with an increased incidence. Various factors are known to influence the plasma levels of HDL-C.[7–13] There seems to be a direct correlation between the low-density lipoprotein cholesterol (LDL-C) and coronary heart disease (CHD) but it is said to be less consistent compared to inverse correlation existing between HDL-C and CHD.[4] There is definitive alteration in the lipid metabolism of leprosy patients as has been shown by many workers.[14–21] Atherosclerosis and CHD appear to be very uncommon in leprosy patients.[26–28] Although there have been many reports regarding general serum

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lipid status of leprosy patients, no one has so far attempted to find out the HDL-C which can offer a better explanation of the hitherto unexplained difference in CHD prevalence and incident rates in leprosy patients. The present study is the continuation of our earlier work.[20]

Materials and methods

Ninety-three cases were included in this study. All were male and none of them had any previous clinical record of cardiovascular involvement. Factors known to affect lipid metabolism like alcohol, smoking, diet, etc., were carefully taken into account when selecting the cases. They were clinically diagnosed and divided into three groups. Group I. Twenty-five cases of untreated lepromatous leprosy, Group II had 46 cases of treated lepromatous leprosy, and Group III consisted of 22 cases of healthy contacts of lepromatous leprosy. All of them belonged to the same socio-economic status. Each group was subdivided into three age groups: (a) 30–39 years, (b) 40–49 years, and (c) 50–60 years. Treatment included administration of dapsone, clofazimine or rifampicin but none of the patients were given steroids or any other drug known to affect lipid metabolism.

Fasting blood samples were collected and fresh sera were used for analysis. Separation of HDL fraction and estimation of cholesterol in that fraction were carried out according to the method of Vikari.[22] Twelve per cent (w/v) PEG-6000 was used as a precipitating agent. But instead of adding equal volume of the precipitating agent to the serum, double the volume was added, i.e. to one part of serum two parts of 12% PEG-6000 were added in order to get maximum precipitation of LDL-fraction. Total cholesterol was estimated by the method of Zak *et al.*[23]

Results and discussion

It was found that the HDL-C was significantly higher in group Ic compared to control group III ($P < 0{\cdot}05$), even though all other age groups tended to show a marginal increase in values. After treatment, again the 50–60 years group (IIc) presented significantly higher value of HDL-C ($P < 0{\cdot}05$).

After treatment, in group IIc there was an increase in HDL-C compared to that of group IIIc but there was not any marked change from the untreated patients of the same age group. The statistical analysis and comparison of groups I and II show that no importance could be attributed to the effect of therapy *per se*.

The values of the ratio of HDL-C to total cholesterol were significantly higher in all subgroups of groups I and II compared to the corresponding results of control group III. The results of the present study are given in Table 1.

Table 1. High density lipoprotein cholesterol analysis in leprosy patients and healthy controls

Clinical condition	Age group (all males)	Serum total cholesterol (TC) mg%†	HDL-cholesterol (HDL-C) mg%†	HDL-C/TC
1 Untreated	(a) 30–39 (14)	113 ± 22·8	29·48 ± 10·59*	0·258 ± 0·061 ($P < 0·05$)
lepromatous	(b) 40–49 (7)	120 ± 18·6	24·11 ± 4·87*	0·203 ± 0·007 ($P < 0·05$)
leprosy	(c) 50–60 (4)	138 ± 16·4	60·25 ± 4·92 ($P < 0·05$)	0·436 ± 0·014 ($P < 0·02$)
2 Treated	(a) 30–39 (26)	118 ± 21·8	30·60 ± 7·00*	0·250 ± 0·014 ($P < 0·05$)
lepromatous	(b) 40–49 (12)	123 ± 22·4	42·75 ± 8·52 ($P < 0·01$)	0·346 ± 0·006 ($P < 0·02$)
leprosy	(c) 50–60 (6)	150 ± 17·8	68·88 ± 6·64 ($P < 0·05$)	0·440 ± 0·009 ($P < 0·02$)
3 Healthy	(a) 30–39 (11)	140 ± 16·8	23·46 ± 3·38	0·177 ± 0·014
contacts of	(b) 40–49 (4)	150 ± 17·5	20·06 ± 9·16	0·123 ± 0·044
lepromatous	(c) 50–60 (7)	158 ± 24·8	40·62 ± 3·95	0·255 ± 0·015
leprosy (control cases)				

* Statistically not significant.

† Standard deviation of the mean values. Numbers in parentheses indicate number of cases studied.

It is well known that compared to a normal population the prevalence of CHD due to atherosclerosis is much less in leprosy patients.[26, 28] This might be due to their favourable HDL-C/Total cholesterol ratio and higher HDL-C levels than the controls as of our study. Heart, large blood vessels and gall bladder are somehow not affected by leprosy. There are no references in the literature regarding the involvement of heart and the formation of atheroma in big vessels.[26, 28] Documented reports for the involvement of cardiovascular system are (a) specific endocarditis due to rapidly growing chromogenic mycobacteria, and (b) specific allergic vasculitis and phlebitis, both cited.[28] However, peripheral arteries and veins reveal sclerosis. Two cases of definitive cardiac involvement in lepromatous leprosy have recently been presented[28] where again the biochemical findings are not complete and that no data are presented on the cholesterol and lipoprotein levels. They speculated that leprosy might have affected the coronary vessels giving rise to CHD. Recent studies have shown that HDL is an independent risk-lowering factor.[9, 24] Higher levels of HDL-C may be protective against the development of atherosclerosis and hence CHD. The following explanations[6, 25] have been provided to explain the role of HDL-C as a protective factor.

(a) Higher concentrations of HDL-C prevent deposition of cholesterol from LDL by blocking the latter's receptors and hence its uptake by endothelial cells.
(b) HDL provides a carrier to transport cholesterol from peripheral tissues to the liver where it is catabolized and excreted.

(c) HDL prevents the accumulation of cholesterol esters inside cells, especially those of the reticulo-endothelial system which phagocytose red blood cells and other dying cells whose membranes contain cholesterol.

So far as our understanding goes, there have been no reports on the effects of dapsone, clofazimine or rifampicin affecting the lipid metabolism in leprosy patients. Our present study has not shown any significant change in HDL-C levels after the patients have commenced taking these drugs. Even though group Ic showed higher values for HDL-C the number of cases we could investigate was only four and this very small number makes our interpretation difficult. More information can be obtained if a controlled study is carried out to find the effect of various anti-leprosy drugs on the lipid metabolism of the patient. It would be useful to carry out an indepth epidemiological study to compare the prevalence of CHD and the usefulness of HDL-C in leprosy patients.

Acknowledgment

The secretarial assistance of Miss Madhu Kapoor is gratefully acknowledged.

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Lepr Rev (1984) **55,** 173–176

Ulnar nerve calcification and abscess formation in two cases of primary mononeuritic leprosy

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Accepted for publication 31 October 1983

Summary Since 1980, four patients have presented at the Shantha Bhawan and Patan Hospitals in Nepal with nerve abscesses. This paper describes the clinical, radiological and surgical operation findings in two of these patients who had ulnar nerve calcification.

Introduction

Although probably not uncommon in practice, few cases of peripheral nerve abscess in leprosy patients have been reported. Although occurring mainly in tuberculoid forms of leprosy, abscesses have been reported[1, 2] in lepromatous patients; Malaviya *et al.* recently reported six cases and recorded 11 others.[3] In the past 3 years, four patients have been seen with nerve abscesses at the skin clinics at Shantha Bhawan Hospital and Patan Hospital in Nepal. In this communication we report two cases of primary mononeuritic leprosy presenting with nerve calcification and subsequent nerve abscess formation.

Case report 1: A.L.H. No. 7070

A 30-year-old Nepalese male employed in Kathmandu presented at the skin clinic, Shantha Bhawan Hospital on 24.1.80 with acroparaesthesia of the left hand. The left ulnar nerve on palpation was found to be uniformly enlarged with no localized tenderness. There was no sensory deficit. Voluntary muscle test of the left hand showed an early low ulnar palsy with weakness Grade III of the adductor digiti minimi, dorsal interossei and the lumbricals II and IV. No skin

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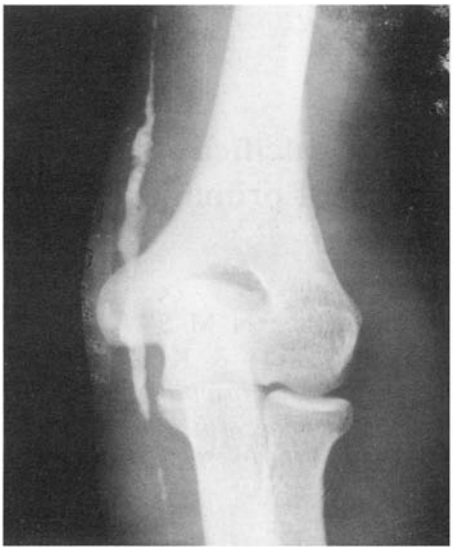

Figure 1

lesions were found. Skin smears for AFB from four sites were negative. A clinical diagnosis of primary mononeuritic leprosy was made. X-ray of the left arm showed a linear radio-opacity suggestive of calcification in the left ulnar nerve (Figure 1). Dapsone 50 mg daily was prescribed. At the follow-up clinic a month later the patient presented with a painful swelling of the left elbow joint. Examination showed a tender localized fusiform swelling of the ulnar nerve proximal to the medial epicondyle. An X-ray of the left arm was suggestive of an ulnar abscess (Figure 2). Surgical decompression and internal neurolysis of the left ulnar nerve was carried out under steroid cover.

The nerve abscess was gently curetted. The caseous content of the abscess was negative for AFB smears. Steroid cover was continued post-operatively. Subsequent sensory and voluntary muscle tests showed no significant change from the preoperative recording.

Case report 2: A.L.H. No 6896

A 25-year-old male Nepalese from Bara district presented at the Shantha Bhawan Skin clinic on 18.10.79 with a right ulnar palsy. He had been diagnosed as a case of tuberculoid leprosy at Duncan Hospital, Raxaul, India and was treated with dapsone 100 mg daily for a month. On examination no skin lesions were found. The right ulnar nerve was thickened but not tender. There was a fusiform, fluctuant swelling over the right ulnar nerve proximal to the medial epicondyle. The right hand showed a high ulnar palsy. Sensory and voluntary muscle tests

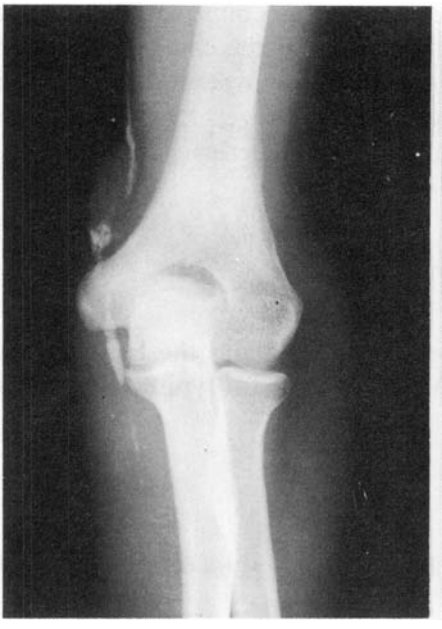

Figure 2

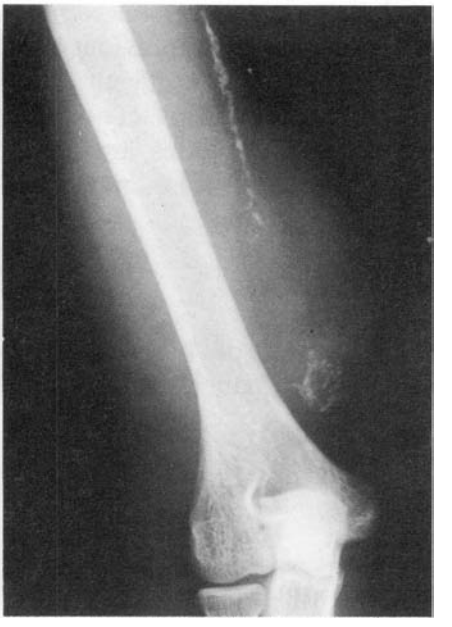

Figure 3

showed a sensory deficit along the distribution of the ulnar nerve and complete paralysis of the flexor carpi ulnaris, flexor digitorum profundus, III and IV, adductor digiti minimi dorsal interossei I, lumbricals III and IV. X-ray of the right elbow showed a linear radio-opaque shadow suggestive of calcification along the right ulnar nerve (Figure 3).

Skin smears for AFB were negative at four sites. A clinical diagnosis of primary mononeuritic leprosy was made and he continued to take dapsone 100 mg daily. He refused hospitalization at that point.

Internal neurolysis was done on 19.3.80 under local anaesthesia. The ulnar abscess was gently curetted. The caseous content of the cavity was negative for AFB smears. In this case there was no steroid cover either pre- or post-operatively. On 1.10.80 a lumbrical replacement of the right hand was successfully carried out using the extensor carpi radialis longus as the motor element and a free graft from the fascia lata.

Discussion

In leprosy, the causative organism, *Mycobacterium leprae* is believed to enter the site of predilection, the peripheral nerves, long before skin lesions appear. Although there is continuing debate about its significance and possible relation to previous skin lesions (no longer visible at the time of first presentation), primary

neuritic leprosy is well recognized in India[4] and other countries. We were unable to obtain any history of previous drug treatment in the cases described in this paper. Classification was difficult; although the lepromin reaction was negative in both patients, there was in fact no other evidence to suggest lepromatous leprosy. Peripheral nerve abscesses are known to those experienced in leprosy, but calcification, as in this case, appears to be rare.

Acknowledgments

We thank the staff of Anandaban Leprosy Hospital and the Leprosy Mission International for financial support and Mr M O Jacob for typing the manuscript.

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Domiciliary and Field Work

Laboratory services in the context of primary health care. ***WHO Chronicle*****, 33, 334–7 (1979)**

The summary of this 4-page article reads '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 connection, WHO has prepared a 20-page document "Laboratory services at primary health care level".' The introduction draws attention to the regrettable fact that laboratory services in developing countries are usually only well established at the central, rather than the peripheral level, but that an attempt has been made to change this pattern in Indonesia, Malaysia, the Sudan and Cameroon. The main headings in the article are: the health centre laboratory; essential laboratory tests for use in the health centre; laboratory services in a primary level hospital; collection and despatch of laboratory specimens and training of laboratory workers. The table of essential tests is of considerable interest because of its brevity and simplicity; only 13 are listed and 2 of these (for sputum in TB and skin smears in leprosy) involve the Ziehl–Neelsen stain. Available from Health Laboratory Technology, WHO, 1211 Geneva 27, Switzerland.

Manual of Basic Techniques for a Health Service Laboratory. **WHO, Geneva, (1980) US $13.50**

This is a comprehensive manual of 478 pages, plus index, covering: general procedures; parasitology; bacteriology; serology; mycology; examination of urine; cerebro-spinal fluid; haematology; blood chemistry and blood transfusion. It is profusely and extremely well illustrated with black, white and grey-shaded drawings and diagrams. Section 31 describes the hot method, for staining tubercle bacilli with Ziehl–Neelsen; Section 32 the cold method, using Kinyoun stain; and Section 33 the examination of leprosy bacilli with a modified Ziehl–Neelsen, using a cold method (only). The precise composition of all the reagents involved in these procedures is given in a section at the end of the manual. (The figures at the top right-hand corner of page 263, for the numbers of leprosy bacilli seen in 1 field, 10 fields or 100 fields range from 0 to 5 and do not correspond to the widely used Ridley scale for the Bacteriological Index; BI.)

A Medical Laboratory for Developing Countries. **M. King (1973)**

A paperback of *c* 70 pages, with a vocabulary index (mainly of technical and medical terms). It is extremely well illustrated, with hundreds of line drawings and diagrams and also has 107 colour plates of microscopy in haematology, helminthology and other subjects. The main sections cover: equipment; making the laboratory ready; records and specimens; weighing and measuring; the microscope; blood; urine; cerebro-spinal fluid; stools; some other specimens; blood transfusion and, finally, a chapter for pathologists, stores officers and medical administrators. Eight pages are devoted to the examination of smears in leprosy, beginning with an outline of the classification of leprosy with some indications of where bacilli are likely to be found. The skin-smear technique is fully illustrated and there is a detailed description of the bacteriological and morphological indices. Price US $14.00; English Language Book Service (ELBS) countries US $4.50). Oxford University Press.

A Medical Laboratory Manual for Tropical Countries. **Monica Cheesbrough (1984)**

Section 44.3 deals with the leprosy bacillus, covering: classification; microscopy; the indices; collection of skin smears; relapse; nasal smears; noseblows; biopsies; staining; interpretation and records. The author has kindly supplied the following information about her organization—'Tropical Health Technology (THT) Ltd' which has been formed to help developing countries by sharing 'our knowledge and helping to transfer appropriate medical laboratory technologies especially in the fields of publication and equipment. It also ensures the continuity of the manual project for which money was donated. Our main activity in the publishing line is to produce the three reference training manuals (Vols I–III), a health centre manual, loose-leaf laboratory diagnostic sheets (covering the major diseases), all using artwork and knowledge originated with Vols I–III. Publishing programme takes us up to the end of 1984.

In the equipment line, our major work is to design, manufacture and distribute a good low-cost (self-servicing) microscope with the aim of having it at least assembled in developing countries. We also hope to produce design drawings for smaller much-needed items of laboratory equipment for manufacture locally as well as here in UK at low cost. We also advise laboratory workers overseas and those going overseas and generally try to assist in whatever way we can.

These volumes can be obtained directly from Tropical Health Technology, 14 Bevills Close, Doddington, Cambridgeshire, England PE15 OTT. Price US $12.50.

0305-7518/84/055177+02 $01.00

Leprosy for laboratory workers, Ponape Hospital, Ponape, Caroline Islands. Carol Murray (1982)

The author has kindly submitted this 26-page manuscript (in draft for further development), which has been used locally in Ponape for the training of laboratory personnel and is still in the stage of revision and development. It covers all basic steps in the examination of smears and is illustrated with line drawings which are in keeping with the equipment and techniques in use in this area. The staining techniques are those used at the USPHS Hospital in Carville, USA.

Technical Guide for Smear Examination for Leprosy by Direct Microscopy

Published by the Leprosy Documentation Service (INFOLEP), Royal Tropical Institute, Mauritskade 63, 1092 AD Amsterdam, The Netherlands. Requests for single copies should be sent to: The Leprosy Mission International, 50 Portland Place, London W1N 3DG. Requests for bulk orders may best be made through representatives of ILEP; the International Federation of Anti-Leprosy Associations. Please note the following errata—Inside cover: list of ILEP members; the correct title is International Federation of Anti-Leprosy Associations, *not* Organisations. The title 'Amici dei Lebbrosi' should be changed to: Associazione Italiana 'Amici de Raoul Follereau'. Page 11: under 1.4, line 10 of the paragraph at top left, the word 'these' should read 'there'. Page 11: Under 1.6. in the first main paragraph, the section reference 2.7 should read 2.8. Page 24: under 3.2.4, the percentage of alcohol should read 70% *not* 95%. Page 25: under 3.3, item i) the period of staining with methylene blue should be 1 minute *not* 3 minutes. Page 26: under 4.1, lines 4 and 5; the figure in brackets should read (× 100) *not* (× 40 and × 100). Page 28: under 4.3.3, fifth line up from the end of the page, omit '. . . . and percentages. . .' It should read 'to express the numbers of solid, fragmented and granular bacilli separately as percentages.' Page 29: under Figure 8, line 3 of the caption; the figure for length should read '. . . between 2 and 8 microns. . .' *not* '. . . 1 and 8 microns. . .' In the one from last line, μ should read 1 μ. Page 31: in the table in Appendix 1, the average for Fatima d/o Hussein under F% should be 2, *not* 0. Page 34: Appendix IV; this diagram has been reproduced with the permission of Dr Gjalt Boerrigter, Malawi, from *Leprosy Review* (1983), *54,* 115.

The Unquiet Eye; a Diagnostic Guide. A J Bron

This is a 98-page booklet with 79 colour prints and a glossary. Some of the points in the booklet are also discussed by Mr Bron in a filmstrip 'The Unquiet Eye' (18 minutes). The main headings are: a guide to techniques; interpretation of symptoms and signs; dry eye; ocular trauma; subconjunctival haemorrhage; conjunctivitis; keratitis; anterior uveitis; angle closure glaucoma; episcleritis and scleritis; the red eye with proptosis; the red lid; summary of treatment; ocular screening by the general practitioner; anatomy; list of useful diagnostic equipment. This is not a book for the specialist and it has not been assembled with third world or tropical diseases in mind. Nevertheless, it is full of information and superbly illustrated. There is no charge and *bona fide* applicants should contact Glaxo Laboratories Ltd, Greenford, Middlesex UB6 OHE, UK, or their local representative for the booklet and/or filmstrip.

Cristoffel Blindenmission; the Local Production of Eye Drops

An A4 paperback, 18 pages, typed sheets, it is intended as a set of practical notes for rural hospitals and comes from the African Region Medical Office of this organization, P.O. Box 1363, Moshi, Tanzania. No charge is stated but we advise paying at least for the cost of postage. The opening paragraph of the introduction explains that the intention is to give information which will enable people to produce their own eye drops locally, at a cost which is often only 10–20% of the ready-made manufactured product. The early sections describe: materials required, including advice on bottles, droppers, basic chemicals, preservatives, antibiotics; the production of distilled water; sterilization by autoclaves; weighing. The ensuing notes on the use of eye drops cover mydriatics, myotics, local anaesthetics, antibiotics, steroids and artificial tears. Detailed information is given on the prescription and production of drops, and the text ends with some notes on eye ointments and drugs that lower intra-ocular tension. This is a supremely practical document which should be studied by all who are concerned with the diagnosis and treatment of eye diseases in the tropics. The Africa Region Ophthlamic Consultant of the Cristoffel Blindenmission has offered to answer questions, sent to the above address.

Teaching Leprosy to Medical Students in Liberia

We gratefully acknowledge the 1982–83 Annual Report of the National Leprosy Control Programme in Liberia and note with particular interest the initiative which has been taken to design a programme for the teaching of leprosy to medical students. Professor Togha, Chairman of the Department of Public Health and Preventive Medicine and Dr J C Johnson, Director of the National Leprosy Control Programme, have recorded their plans for an outreach programme to sensitize final year medical students to early diagnosis and treatment of leprosy, thus aiming at the reduction of the prevalence and morbidity of leprosy in Liberia—and its eventual eradication. There will be intensive training at Ganta Leprosy Centre in January and February each year. We look forward to hearing of progress and hope that this initiative with medical students (who are perhaps even more important than qualified doctors in this context) will be taken up in other countries. Contact Dr J C Johnson, The National Leprosy Control Programme, P.O. Box 1240, Monrovia, Liberia, Africa, for further information.

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Reports, News and Notes

Heiser Program for Research in Leprosy, 1984

Once again this program has sent details of the awards which are offered. These fall under the headings of post-doctoral research fellowships, research grants and visiting research awards. The Scientific Advisory Committee includes Maclyn McCarty, W Lane Barksdale, Barry Bloom and Charles Shepard. Applications and enquiries to Mrs Barbara Hugonnet, Director, Heiser Program for Research in Leprosy, 450 East 63rd Street, New York, New York 10021, USA.

Derrick Dunlop Travelling Fellowship, 1984

Applications are now being invited for the Derrick Dunlop Fellowship, which was created by the Winthrop Foundation and is administered by the Royal College of Physicians, Edinburgh. The Fellowship is open to Fellows and Members of the Royal Colleges of Physicians in the United Kingdom and Ireland, and provides up to £5,000 over a period not exceeding 2 years. The extent of tenure into the second year will depend upon the submission of a satisfactory interim report at the end of 12 months.

It is envisaged that the Fellow will already occupy a full-time university, National Health Service or other salaried post and will use his Fellowship to travel to centres at home or abroad. Proposals for studies in Clinical Pharmacology, Therapeutics and related disciplines, including national differences in prescribing practice,would be supported. The studies should be of a standard that might be expected to lead to a submission for the degree of MD or PhD, or for publication.

Applications should include a curriculum vitae, a synopsis of approximately 1,200 words describing the proposed study, and the names of two referees. Intending applicants should apply for the appropriate form to the Secretary, Royal College of Physicians, 9 Queen Street, Edinburgh EH12 1JQ.

LEPRA Prize Essay Competition for Medical Students in the UK, 1984

Following the tradition of the past 10 years or more, LEPRA is organizing a prize essay competition for UK medical students in 1984, with the following titles. 'Monoclonal antibodies and recombinant DNA technology: present and future use in leprosy and tuberculosis' OR 'Leprosy will be most expediently controlled by the continued use of vertical, specialized programmes' OR 'Leprosy will be most expediently controlled by the use of fully integrated programmes which make use of the primary health care approach'. Full details will be sent to all medical schools in the UK early in 1984. Enquiries may also be directed to the Editor of this Journal, or to LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU.

Takemi Fellowships in International Health

The Takemi Program in International Health invites applications from promising graduates of Advanced Degree programmes and mid-career professionals with relevant backgrounds, for Fellowships in Research and Advanced Training on critical problems in international health, especially those concerned with less developed countries. For information write to Professor David E Bell, Acting Director, Takemi Program in International Health, Harvard School of Public Health, 665 Huntington Avenue, Building 1, Boston MA 02115, USA.

Raoul Follereau Grant for Leprosy Research

The Italian Leprosy Relief Association 'Amici di Raoul Follereau', an organization for international health cooperation, offers a grant of US $20,000 for leprosy research, named after Raoul Follereau, to a young research worker in a European department. The object of the grant is to stimulate the undertaking of original research in the field of leprosy in a research department in Europe. Further details may be obtained from 'Amici di Raoul Follereau', via Borselli, 4-40135 Bologna, Italy. Tel. 051/423809-433402.

Histopathology Services for Developing Countries

Professor Michael Hutt retired from St Thomas' Hospital in London in September 1983 and recently issued the following letter concerning histopathology services, which include the examination of biopsies for leprosy:

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'For the last 15 years the department of Histopathology at St Thomas' Hospital has provided a free, postal, diagnostic service for a number of hospitals, both government and mission, in developing countries. It was originally envisaged that the need for such services would decrease as they were built up locally. For a variety of reasons, differing from country to country, this has not happened and the need is still there and likely to continue. To meet these problems and to provide histopathological expertise in parasitic, communicable and other tropical diseases in the UK a new consultative histopathologist post has been created jointly with the London School of Hygiene and Tropical Medicine and University College Hospital Medical School. This post has just been filled by the appointment of Dr S B Lucas who has spent 2 of the last 4 years in this unit and 2 in the Pathology Department at Nairobi. My own full-time post will terminate in September when I retire, though I will continue my involvement with developing countries on a part-time basis.

Dr Lucas is keen to maintain or increase the diagnostic services for tropical countries and we hope to raise funds to cover the expenses of such work.

As from 6 April 1983, I would be grateful if you could re-route your postal specimens to him:

Dr S B Lucas, Department of Morbid Anatomy, School of Medicine, University College London, University Street, London WC1. Telephone 01-387 9300.

I hope to remain in contact with you through my association with Dr Lucas and I am sure that he will provide you with an excellent service.'

M S R Hutt, *Professor of Geographical Pathology*

Bureau for Overseas Medical Service (BOMS), London

This is a charity for health workers who are interested in working in the Third World countries of Asia, Africa, the Caribbean and South America. BOMS offers career advice and information about jobs in hospitals, clinics, missions, primary health care units and teaching establishments. Enquiries from doctors with provisional or full registration in the UK are welcomed. The BOMS register has been enlarged to include all health workers, including paramedical workers with state registration and 2 years' working experience. Nurses must be SRN with a higher teaching qualification.

Anyone interested in joining the register or knowing of a vacancy for a health worker in the Third World is invited to contact Colin Jacobs, Secretary, Bureau for Overseas Medical Service, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, telephone 01-636 8636 ext. 232.

ILEP Catalogue on Training 1984

ILEP (International Federation of Anti-Leprosy Associations) has issued a catalogue of training centres in various parts of the world, which gives full details of the courses offered, main subjects taught, etc., English and French text. The centres include those in ALERT, Ethiopia; Bamako, Mali; Bauru, Brazil; Carville, USA; Fontilles, Spain; Karigiri, India; Mexico City, Mexico; Yaounde, Cameroon; and Dakar, Senegal. Copies are available from ILEP, 234 Blythe Road, London W14 OHJ, or from ILEP representatives

MD Thesis with High Commendation and Gold Medal for Dr M Elizabeth Duncan, Edinburgh

It is with the greatest of pleasure that we record the award of the degree of MD in the University of Edinburgh, with high commendation and gold medal to Dr M Elizabeth Duncan, for her work on 'A prospective clinico-pathological study of pregnancy and leprosy in Ethiopia'. Following a series of distinguished publications (and there are more to come), this is a richly deserved award for her many years of work, mainly in Ethiopia, on this subject.

Physical Therapy Training Manual, 1983; the Leprosy Mission International

We are extremely grateful to Dr Mrs E S Thangaraj for sending a copy of the TLMI *Physical Therapy Training Manual*, which she has edited. It is published by TLMI at 4th Floor, Sheetla House, 73–74 Nehru Place, New Delhi-110019, India. This is a strongly constructed paperback of 122 pages, very well presented and a pleasure to read. A series of clearly stated objectives (1–13) form the basis of the text and there are then 10 annexures on clinical features, nerve palpation, nerve damage, neuritis, treatment, plaster work, splints and case assessment. Appendices follow on footwear, tools, ulcers, dressing, POP casts and dorsal incision. This manual reveals the depth of experience and knowledge of some of the best people working in physical therapy in leprosy and it should be of enormous practical value.

AGFUND; Arab Gulf Programme for United Nations Development Organizations

This organization was created in 1981 by seven Arab Gulf States (Bahrain, Iraq, Kuwait, Oman, Qater, Saudi Arabia and the United Arab Emirates). Its objectives are to support development and social efforts in developing countries; to organize and coordinate assistance by Arab Gulf States to activities of UN agencies and their development programmes; to direct this aid towards specific development projects benefiting the underprivileged populations. Priority is given to projects of a humanitarian and developmental nature. WHO Press Release of 22 April 1983 records that large sums of money had been allocated to: 1 the prevention of blindness in Bangladesh, Mali and Nepal; 2 TB control programmes in India, Morocco, Pakistan, Panama and

Upper Volta; and 3 to maternal and child health, including family planning in Bahrain. Offices are at P.O. Box 22912, Muharraq, Bahrain and P.O. Box 18371, Riyadh, Saudi Arabia.

Royal National Institute for the Blind, London, Catalogue of Apparatus and Games

The Royal National Institute for the Blind, 224 Great Portland Street, London W1N 6AA (Telephone 01-388-1266), produces three documents which give detailed information about apparatus, games and specially designed articles for the blind. The first is a simple list of publications in print, prospectuses for various schools, training centres and special centres for the blind. The second is a price-list of all articles which are available from the RNIB, dated April 1983. And the third is an illustrated catalogue of 67 pages, with index, which describes a remarkable range of apparatus which is available from this organization—if not free, at very reasonable prices, and with reductions for certain categories of applicant, including blind people in the UK. The main subject matter includes: Braille equipment of all kinds; writing frames, stationery devices; clocks, watches and timers; games; maps and globes; mathematical apparatus; rules and measures; tools and aids for carpenters, the deaf–blind, gardeners, handicrafts, householders, musicians, physiotherapists and typists. Those unfamiliar with the world of the blind will be amazed at the breadth and ingenuity of the apparatus and articles described in this catalogue. Whilst many, perhaps the majority, have been developed for blind, or partially-sighted people in developed countries, others could be valuable anywhere in the world, though they might well need adaptation to local conditions. If applying to the above address for these documents, pre-paid postage would be appreciated.

Clinical ophthalmology: a Text and Colour Atlas. James L Kennerley Bankes

The author works in a London teaching hospital and the book has been written 'for those requiring some specialized knowledge of opthalmology in their work and it is hoped that the needs of medical students, general medical practitioners and those beginning a career in ophthalmology will be met'. As the publishers state in their 'promotion' summary this is indeed a superbly illustrated atlas. The chapter headings include: examination of the eye; use of instruments; refractive errors, rapid changes in refractive errors; colour and vision defects; age changes in the eye; eyelid conditions; watering of the eyes; lacrimal disease; red (inflamed) eyes; eye injuries and first aid; strabismus (squint); cataract and lens displacement; glaucoma; orbital disease; fundus conditions; optic nerve and visual pathway disorders. There is a full index. No attempt is made to deal with tropical conditions in the eye but those embarking on ophthalmology in any part of the world should surely find this text-atlas of the greatest value and, by comparison with most medical books these days, it is excellent value. Price £9.95($15.00 US) 125 pages, reinforced paperback, quarto, Churchill Livingstone, 1982

The Council for International Organizations of Medical Sciences (CIOMS)

A very successful Round Table was held in Geneva on 7–9 December 1983, under the auspices of the CIOMS of which the International Leprosy Association is a founder-member. The international participants were representative of very diverse interests—from research scientists to animal welfare organizations, and from pharmaceutical companies to WHO officials. It was news to many of the participants that leprosy is still indebted to the use of experimentally infected animals for much of the research that has resulted in new knowledge and better treatment regimens. The wide use of the elegant mouse foot-pad inoculation technique in proving drug resistance (both secondary and primary) and the presence of persister organisms, appears at present to be mandatory: there are no alternative methods. Furthermore, the provision of quantities of *M. leprae* from experimentally infected armadillos is crucial for the development of a specific protective vaccine or of immunoprophylactic procedures. As the result of the papers presented at this Round Table and the ensuing discussions, a set of guidelines will be drawn up and widely distributed to governments, research institutes, animal welfare organizations, etc., to form the basis of practice, and perhaps, legislation.

Sasakawa Memorial Health Foundation, Japan.

We gratefully acknowledge receipt of the following documents:
1 *Sasakawa Memorial Health Foundation, 1982.* Background of establishment. Basic principles for our project formulation; mode of action; programme planning; outline of programme (fact-finding missions and consultations, international seminars, workshops and conferences, research, training of health workers in leprosy, technical cooperation by the experts, supply of drugs and equipment, other activities). This is an 18-page booklet, published by a grant from the Japan Shipbuilding Industry Foundation (JSIF).
2 *Basic Epidemiological Indicators for Monitoring Leprosy Control* by M F Lechat and M Vanderveken, 1983. This is a 24-page booklet from the Department of Epidemiology in the University of Louvain in Brussels, packed with valuable information under the main headings of: 1 Crude rates—prevalence, incidence; 2 Specific rates; and 3 The trends in incidence rates. There is a list of 32 references.
3 *Leprosy in Japan, 1983.* Edited by Dr Fujio Ohtani, Ministry of Health and Welfare. The main headings are: Historical background; leprosy situation in Japan (mainland and Okinawa) and conclusions. This is a 28-page booklet, which includes Appendices of the location and names of leprosaria in Japan, the Leprosy Prevention Laws and the Global Geographical Distribution of Leprosy from WHO Weekly Epidem. Rec., No 3, 1979.
4 *English Publications of the Foundation, 1983.* This is the complete list of: A Proceedings of the International Workshops; B Proceedings of other meetings (National and International), and C Other publications, including those on Sasakawa fellowships, *Health for All by the Year 2000* (Dr H T Mahler), the *Way Toward the Eradication of Hansen's Disease* (Professor M F Lechat), *Leprosy In China* (Dr S G Browne) and the *1981* and *1983 Atlases of Leprosy*, both prepared in the Philippines.

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Letters to the Editor

AN ALCOHOL TEST FOR SUPERFICIAL CUTANEOUS SENSIBILITY

Sir,

A number of tests have recently been devised to aid the detection of anaesthesia on the skin in patients with leprosy. Although previously published, (*Manual de Leprologia* by Bernardo Rojas, Concepcion, Paraguay, 1977), I would like to draw attention to a test using alcohol on the skin which may be of value in this context. All that is needed is a glass dropper with some alcohol. Holding the dropper 15 cm above the skin, one drop of alcohol is allowed to fall on the surface of the skin. If the patient has normal responses, two distinct sensations are perceived almost simultaneously. First he feels the physical contact of the drop, closely followed by a distinct feeling of coldness. If there is a lesion on the skin with definite diminution of sensation, the patient registers neither the first contact nor any feeling of coldness, though the latter may be noted if the alcohol spreads out on the skin to adjacent areas with normal sensation. Our experience is that this test dispenses with the use of hot and cold tubes, sensory testing with sharp or blunt instruments or cotton wool. As with other tests for this purpose in leprosy, it should be performed with the eyes covered.

B ROJAS

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THE EFFECT OF CORTISONE ON *MYCOBACTERIUM LEPRAE*-INFECTED MICE

Sir,

In my article titled 'Jacinto Convit and the Leprosy Vaccine', which appeared in *Interciencia*, Vol. 7, September–October 1982, I wrote: 'I later worked with Martin Vegas, in a laboratory set up in his house's garage, at a time when the University laboratories had been closed down by Pérez Jiménez' dictatorship, unsuccessfully trying to infect with *M. leprae* mice treated with huge doses of cortisone, with a view to enhance (infectivity), in analogy with what happens with tuberculosis infectivity . . . (these negative results were never published).'

You now kindly ask me to record some of our experiences, and I gladly do so, in the briefest possible manner. I cull the following from the now yellowed protocol pages, which we have kept.

Vegas and I began our experiments on 15 December 1951. We studied six groups of 20 white mice each. Injections of cortisone and solvent were started 6 days before inoculation. Experimental groups were as follows: 1) Intraperitoneal inoculation with macerated *Mycobacteria*-rich material obtained from lepromatous leprosy cases; cortisone 0·1 mg daily subcutaneously, 2) subcutaneous inoculation plus 0·5 mg cortisone daily, 3) intraperitoneal inoculation plus daily injection of cortisone solvent, 4) subcutaneous inoculation plus daily injection of cortisone solvent, 5) intraperitoneal inoculation without any treatment 6) subcutaneous inoculation without any treatment.

Mice were observed daily. Those that died were immediately autopsied and examined. Smears and histological sections were made from testicles, liver and spleen. Experiments were terminated in June 1952, when all surviving mice were sacrificed and their organs examined.

The results were briefly as follows: there was no difference in mortality between the cortisone-treated and the untreated mice. Nor was there any difference in the lesions observed. Both in cortisone-treated and untreated mice,occasional *Mycobacterium* globi and isolated bacteria were observed in the skin, liver and spleen, with no apparent increase in the cortisone-treated animals. The feeling was that *Mycobacteria* in these animals acted as a foreign body rather than as truly infective material. It was concluded that cortisone did not lead to infectivity by *Mycobacteria* in mice, under the conditions of the experiment.

Had we been able to demonstrate infectivity by *M. leprae* under the effect of cortisone, this would have been a breakthrough in the pre-armadillo days. As it is, the findings are only of historical interest, and I am presenting them as such.

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DAPSONE-RESISTANT LEPROSY

Sir,

Leprosy Review must be congratulated for the timely tribute to Dr R J W Rees, in the special issue of June 1983. Dr Rees' dedication to the scientific battle against *Mycobacterium leprae* is an example to researchers all over the world.

The same special issue of June 1983 carried an article by J M H Pearson entitled 'Dapsone-resistant leprosy', on pages 85S–89S. Before making a few comments, may we indicate some important corrections. In the references cited, the title of the eleventh reference (Almeida *et al.*) is 'Studies on DDS-resistant *M. leprae* in leprosy patients of Gudiyatham Taluk . . .' and not 'Prevalence of secondary dapsone resistance in Gudiyatham Taluk . . .'[1] Secondly, Balraj *et al* (from Gudiyatham Taluk) are represented as having reported a '5-10% prevalence of dapsone-resistant leprosy'. The exact figure reported by them was 2·3%.[2]

Dr Pearson quite rightly points out that the findings of his study in Ethiopia 'rather quickly overshadowed' other reports of dapsone resistance. The reported prevalence of '10–20%', from Ethiopia stands in marked contrast to reports of 2·3 to 6·8% from Malaysia,[3] Costa Rica,[4] Israel,[5] and Gudiyatham Taluk, South India.[2] Since the findings in Ethiopia were 'not the result of formal surveys', and depended on 'cases with clinical suspicion of dapsone-resistant leprosy' being 'referred', some questions arise.

Patients with predominantly dapsone-sensitive *M. leprae* who fail to take dapsone can easily be included among those diagnosed to have 'dapsone-resistant leprosy'. Dr Pearson could perhaps explain how he avoided such misclassification. If investigations continued in Ethiopia after Dr Pearson's departure, the findings would be of interest.

Patients tested for 'primary dapsone-resistant leprosy' are said by Dr Pearson, to have been reported for the first time in 1977. Some papers by Rees were overlooked. In 1967, Rees[6] published data showing that *M. leprae* from previously untreated patients grew in the foot-pads of mice fed 0·1% DDS: roughly equivalent to a daily DDS dose of 1000 mg (1g) in an adult patient. In 1965, Rees[7] reported on the results of feeding DDS, to mice inoculated with *M. leprae* from previously untreated patients: 'The overall result on nearly a hundred foot-pads has been complete inhibition in only 82%.'[7] *M. leprae* from untreated patients were, therefore, found to grow in the foot-pads of mice fed high doses of DDS in some of the earliest tests performed. It is no surprise that such DDS-resistant mutants of *M. leprae* which were detected by Rees[6, 7] in 1965 should again be reported by Pearson[8] in 1977, and should continue to be found wherever they are sought. The spread of DDS-resistant *M. leprae* from treated patients is not the only explanation for DDS-resistant *M. leprae* in untreated patients.

However, Dr Pearson's interesting hypothesis of an 'epidemic of primary dapsone-resistant leprosy' can be evaluated. In areas where suitable records are available, the response to dapsone monotherapy can be compared in recently infected patients and those infected relatively long ago. If those infected recently show relatively diminished response to DDS, Dr Pearson's hypothesis would be strengthened.

We look forward to hearing the comments of Dr Pearson and any workers in Ethiopia who can shed more light on his findings in that country.

The discussion of drug resistance in leprosy must in no way be construed as criticism of multiple drug therapy. On the contrary, only a full discussion will allow crucial questions on drug resistance in leprosy to be answered.

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XII INTERNATIONAL LEPROSY CONGRESS, NEW DELHI, INDIA 20–25 FEBRUARY 1984

Editorial

S G BROWNE
Secretary-General of the Congress, and of the International Leprosy Association

The XII International Leprosy Congress was the best-attended in the long line of such gatherings. It attracted more participants (1460) from more countries (90), and more Abstracts (510) were submitted than at any previous Congress. It is too early to assess its significance in terms of leprosy control, and those who have been bombarded by the plethora of scientific papers over the period of intense activity of concurrent Sessions are perhaps least able to identify the contributions of seminal importance. The Reports of the Workshops, which appear in this issue of *Leprosy Review*, indicate the range and the depth of topics discussed by correspondence between their members over 2 or 3 years, and the final wording that was thrashed out in the days immediately preceding the Congress.

Official interest in the subject was guaranteed by the personal involvement of the Prime Minister of India, Mrs Indira Gandhi, who readily consented to give the Opening Address—a more-than-adequate compensation for having to postpone the agreed date of the Congress. (Mrs Gandhi called a Consultation of Commonwealth Prime Ministers for the period when the authorities had agreed to allow the Congress the use of the meeting rooms at the Vigyan Bhavan Conference Centre.) The President of India graced the Opening Ceremony with his presence, and Mother Teresa was among the participants.

Having got off to a good start, the Congress settled down to real work on the Monday afternoon. In order to fit in the numbers of excellent Abstracts submitted and selected by the President's Reading Committee to be presented as full papers (284 of them), concurrent Sessions had been organized. This was unfortunately necessary, but it did lead to clashes of interest where participants had to choose one of the two sessions they would like to attend. However, the organizers had striven to reduce these possible clashes to a minimum by a deft arrangement of the sessions. The most noticeable exception to the general rule of concurrent Sessions was on the Friday when there were two sessions on the Social Aspects of Leprosy. The Organizing Committee had apparently bowed to pressure from interested parties who wished to emphasize the overriding importance of the non-medical factors in leprosy control. How Raoul Follereau's

heart would have rejoiced! It was he who, at the Tokyo Congress in 1958, belaboured the participants for being more interested in the fate of the experimental mouse than in the plight of the human victim of leprosy.

Since all the Abstracts submitted will be published in a future issue of the *International Journal of Leprosy*, and since that issue will contain the comprehensive Report and Summary of the Sessions that I, as Secretary-General of the Congress, gave to the assembled participants at the Closing Session, readers are referred to that Journal for the details that will not be repeated here.

The presentation by poster of the Abstracts (168) proved more popular than was thought probable. Authors were able to explain their findings whenever they found people interested enough to stop and discuss.

An innovation that was much appreciated was the Teaching Seminars, illustrated by coloured transparencies and diagrams. The commentary was in English, French and Spanish—the official languages of the Congress.The series covered several important aspects of leprosy, and brought generalists and specialists up to date. They proved useful and very popular.

In the following paragraphs, the highlights of the Sessions will be indicated and those contributions likely to prove of general interest.

In the *Clinical Session*, it was reported that in some good leprosy control programmes, the deformity rate among newly diagnosed cases had shown progressive reduction year by year, an observation that suggests that more patients are being diagnosed at an earlier stage: the implication is that there is generally a greater awareness of the cutaneous manifestations of early leprosy and that the treatment being instituted should prevent nerve damage and its sequelae. Practising doctors and medical auxiliaries should become conversant with the range of locally prevalent dermatoses, so as to be able to diagnose and classify more accurately the patients with leprosy presenting at their clinics. The bearing of pregnancy on the appearing of diagnosable leprosy lesions and on the occurrence of reactions was discussed at some length.

The two Sessions on *Treatment* concentrated on the growing menace of secondary dapsone resistance, and the popularization of regimens of multidrug therapy advocated both to prevent and to treat drug resistance. It was generally agreed that rifampicin should form an essential component of any such regimen because of its mycobactericidal properties. The real danger of monotherapy was emphasized by the report of leprosy bacilli resistant to both dapsone and rifampicin.

It is not yet known if the multidrug regimens that are being advocated will prove efficacious both in preventing the emergence of resistant strains of bacilli and in dealing with persister organisms, but we do know that if they are not adopted, then the resulting drug resistance will pose an unmanageable problem in the whole world.

The place of clofazimine in these regimens was recognized, as was its acceptability by lighter-skinned Mongoloid patients.

In spite of secondary dapsone resistance having appeared in 25 countries, and

primary resistance being discovered wherever it is being looked for, dapsone is still an excellent anti-leprotic and should not be lightly discarded.

The Malta Leprosy Eradication Project was referred to, and some doubt was expressed about the hepatotoxicity of its prothionamide component. Thalidomide was reported to be most effective in controlling the skin manifestations and systemic symptoms of some types of acute reaction.

As was to be expected, the (three) Sessions on *Immunology* provided the most popular and the most important forum of the Congress. Workers in many countries are using new and sophisticated techniques for investigating the complexities of the immune response to leprosy infection. A specific phenolic glycolipid has been isolated and identified. Monoclonal antibodies have been synthesized and examined. The search for a protective vaccine continues, with pride of place being apparently accorded at the moment to a mixture of (live) BCG and various moieties obtained from armadillo-derived *Mycobacterium leprae*. The organisms are being purified by novel techniques to rid them of the last traces of contaminating armadillo elements. Now that quantities of such bacilli are available, work is proceeding apace on the identification of *M. leprae*-specific determinants that are recognized by T-cells. The details of the immune response are found to be increasingly complex, and the role of macrophages as well as that of sensitized lymphocytes is the subject of much fruitful investigation.

With the application of ever-increasingly severe criteria for the identification of *M. leprae*, no candidates were admitted, though the successful culture of closely related mycobacteria may eventuate in the identification of some organism that has an antigenic constitution closely resembling that of *M. leprae*. Such an organism could be considered as a possible candidate vaccine if it could be shown to sensitize lymphocytes to recognize and to lyse *M. leprae*.

Much work is proceeding on the characterization of the circulating immune complexes in patients with leprosy reaction.

While much of this new work is of fascinating interest, it is to be hoped that some of it at least will soon be seen to have a bearing on the continuing problem of leprosy control.

The Session on *Surgery and Rehabilitation* was noteworthy in that the gap between the interventionists and the non-interventionists in the matter of the acutely inflamed peripheral nerve in leprosy is evidently narrowing. If anti-inflammatory medical treatment does not lead to rapid improvement (shown by diminutive of local pain and tenderness and swelling), then the nerve sheath should be incised to relieve tension.

Reconstructive surgeons are making significant contributions to neurophysiology as they pursue their researches in nerve damage in leprosy.

Time and again, it was emphasized that if only leprosy were diagnosed early and treated properly, then the great bulk of nerve damage and its unfortunate orthopaedic sequelae would be a thing of the past.

The Session on *Opthalmology* produced some interesting papers on operative

procedures and on the ultrastructure of the eye damaged in the course of leprosy. Involvement of both the facial (VII) and the trigeminal (V) nerves in leprosy poses problems when the insensitive cornea is exposed in paralytic lagophthalmos—a challenge to the practising leprologist.

The perennial questions posed by *nerve damage* in leprosy were brought up during the Session devoted to this theme. The entrapment syndrome was discussed, and the possible reasons for maximum damage at the sites of predilection were examined. Breakdown products of both nerve fibres and *M. leprae* may be involved in the pathogenesis of the damage observed—a condition having parallels with allergic peripheral polyneuritis. One interesting report provided evidence that *M. lepraemurium* could cause damage to peripheral nerves in certain strains of mice. Other workers reported invasion of the central nervous system by *M. leprae* in the heavily infected experimental animal.

In the Session on *Experimental leprosy*, the armadillo was reported to be a most valuable experimental animal. Colonies established in several countries are now the source of *M. leprae* in considerable quantities. The occurrence of infections of wild armadillos by a *M. leprae*-like organism producing a leprosy-like disease is now well established. Recent investigations suggest that this endemic has been present for some time in the southern States of the USA. The 7-banded armadillo in Argentina has been successfully infected with *M. leprae*. Unlike its relatives further north, this animal breeds in captivity.

Although it has long been a canon of leprosy orthodoxy that the disease is confined to humans, the discovery of leprosy in wild armadillos, and more recently in the sooty Mangabey monkey in Africa has shattered a long-held belief.

The other interesting finding reported at the Congress was the experimental infection with *M. leprae* of nude mice and athymic Lewis rats.

More work is proceeding on the genetic and lymphocytic control of resistance to subcutaneous inoculation of *M. leprae*, and on animal models of the molecular biology of the host–parasite relation in *M. lepraemurium* infections in rodents.

The First Session on *Epidemiology and Control* was introduced by an authoritative and wide-ranging statement from the World Health Organization that emphasized the seriousness of the worldwide endemic of sulphone-resistant leprosy. The only way at present available of containing this threat is the reduction in the *réservoir de virus* by multidrug therapeutic regimens consistently applied. In some countries, this programme could usefully be combined with the attack on tuberculosis. From China came an excellent report on the success of control measures, and from Vietnam news of an ambitious programme for the eradication of leprosy. An epidemic of leprosy in virgin soil was reported from a Polynesian island, very reminiscent of the explosive epidemic in Nauru half a century ago.

Attempts are still being made to identify nutritional and hormonal environmental factors that may predispose to the development of clinically diagnosable leprosy.

Perhaps the most important paper presented at this Session concerned the

possibility of leprosy control by means of immunoprophylaxis, using a mixture of BCG and various moieties of *M. leprae*. The enthusiastic advocacy of Venezuelan workers will be tempered by the objective assessment of their results.

Medical auxiliaries need better training in leprosy—this was a message that came over loud and clear. In many leprosy programmes, their diagnosis is more accurate than their attempts at classification; since the duration of treatment recommended depends largely on accurate classification, the standard should be raised and better laboratory cover provided.

The second Session discussed strategies aimed at strengthening case detection activities associated with programmes for Primary Health Care. Subclinical leprosy infection may be much commoner than many imagine, but it is not very important from the epidemiological standpoint.

At this Session, it was reported with some satisfaction that the percentage of newly diagnosed leprosy patients who already have some degree of established deformity is decreasing in areas where good control programmes are in operation.

A potentially useful urine spot test to detect regularity of dapsone intake was described, but it may not be of great practical value in programmes where multidrug therapy is the norm.

Genetic studies in leprosy and the possible linkage of certain histocompatibility antigens (on the HLA system) are helping to resolve the earlier reported discordances. Twin-pair investigations give concordance rates of infection and type of leprosy significantly higher in monozygotic than in dizygotic twins.

Some good papers on the various drugs used in the treatment of leprosy were presented at the Session on *Experimental Therapy*. An important and practical recommendation concerned the value of a monthly dose of rifampicin as being therapeutically effective and less hepatotoxic than intermittent dose regimens with shorter intervals between doses. One case of resistance to clofazimine has been reported, but quite a number of instances of resistance to rifampicin are now known. It would be a tragedy if the efficacy of this valuable mycobactericidal drug were to be impaired by uncontrolled and indiscriminate use.

To accommodate several presentations that did not fit easily into the announced Sessions, time was allotted to the study of various aspects of the *Pathology of leprosy*. The importance of the vascular endothelium in the symptomatology of leprosy was emphasized. One paper suggested that visceral lesions are more common than is generally thought. The well-established observation that leprosy bacilli may leave the intact skin through sebaceous and sweat glands and hair follicles was mentioned. It is more difficult to identify the portal of entry, but recent work incriminates the mucosa of the posterior nasal region.

For the first time in the history of Congress held under the auspices of the International Leprosy Association, two whole sessions—with no competitive concurrent Sessions—were devoted to the *Social aspects of leprosy*. This fact indicates the importance that all leprosy workers now attach to the non-medical,

non-clinical aspects of leprosy. The epidemiology of leprosy cannot be studied apart from its social and cultural milieu, and apart from all the factors of beliefs and assumptions, of language and superstitions, surrounding the disease. Nor can control measures be successfully implemented unless the co-operation of everybody concerned—patients, families, fellow-villagers, the government and medical personnel—is enlisted.

The Session discussed the pros and cons of substituting the term 'Hansen's disease' for leprosy, but was unconvinced by the arguments put forward. The problems and opportunities presented by the WHO slogan 'Health for all by the year 2000', and the present fashionable insistence on Primary Health Care, were discussed in the context of the differing situations in the countries were leprosy constitutes a disease of public health importance.

The Session identified target groups towards which specific health education programmes should be initially directed—medical staff at leprosy institutions and, indeed, all doctors and medical students; the educated patient; and those patients not suffering from the deformities associated in the public mind with leprosy.

There is a regrettable gap between the new knowledge about leprosy and its treatment, and the application of this knowledge to the individual sufferer. So far, many of the latter are not convinced of the effectiveness of leprosy treatment and its success in preventing deformity.

The hope was expressed that at future Congresses it might be possible to welcome the paticipation of leprosy patients in discussions on the social aspects of leprosy; this would give point and dramatic urgency to the theorizing of the pundits.

* * *

As in most congresses nowadays, the Programme for the Sessions was overfull, and there was inadequate time for discussion. Many of the presentations merited immediate examination by groups of interested and knowledgeable critics. The thrust and parry of good debate would add immeasurably to the value of these international gatherings. But the difficulties are immense, almost insuperable. Unless potential participants can ensure that their travel and accommodation costs will be met whether they present papers or not, attendence at future Congresses will suffer; overcrowded programmes do not provide the best environment for unhurried objective examination of important contributions to knowledge.

There is no doubt, however, that the XII International Leprosy Congress will go down in history as the biggest—and perhaps the best—of these gatherings of people from many lands and many scientific and social disciplines engaged in the common task of tackling one of the most redoubtable foes still confronting the human race.

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Pre-congress workshops

From 16 to 18 February 1984, workshops were held on the following subjects: Experimental Leprosy; Microbiology; Immunology; Experimental Chemotherapy; Epidemiology and Control; Teaching and Training; Social Aspects. As on the occasion of previous congresses, the reports were prepared by the chairmen and rapporteurs and distributed to all delegates.

Experimental leprosy

The workshop reviewed advances in the last 5 years in 4 major animal models of experimental leprosy: a, immunologically-intact mice; b, armadillos; c, athymic, nude mice and rats; and d, primates.

Immunologically-intact mice continue to be the experimental leprosy model of choice for determining drug sensitivity of clinical isolates of *Mycobacterium leprae*, for routine determination of viability of *M. leprae*, for determining the bacteriostatic or bactericidal action of antileprosy drugs and other uses. A newer model was presented consisting of an immune tolerant animal following the intravenous injection of 10^7 *M. leprae* in naïve mice. In mice rendered tolerant by intravenous injection of *M. leprae*, intradermal challenge does not result in DTH. Various potential antileprosy vaccines have been used as a means of overcoming this tolerance. With the possible exception of BCG, none have been successful.

Armadillos continue to be utilized primarily for the production of *M. leprae*. Armadillos from the USA consistently are capable of yielding large numbers of *M. leprae* (more than 10^9 bacilli per gram of tissues from liver, spleen and lymph nodes) within approximately 2 years of inoculation with viable bacilli. Wild armadillos caught in the USA sometimes have a variety of other infections including: a, natural infection with *M. leprae*; b, *Sporotrichium shenkii* (up to 63%); c, coryneform organisms; d, cultivable mycobacteria; e, *Trypanosome cruzii*; f, *Salmonella typhimurium*, Coccidiodosis, etc. Natural infection with *Mycobacterium leprae* seems to be found in Texas and Louisiana but not in Florida, USA. Successful breeding of nine-banded armadillos (*Dasypus novemcinctus*) in captivity has occurred in Brazil. Experimental transmission has also been successful with *D. hybridus* in Argentina. This species is of considerable interest since it breeds easily in captivity.

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A number of laboratories around the world are now working with nude mice as a model of lepromatous leprosy. Yields of bacilli as high as 10^{11} per mouse have been reported 18 months after inoculation with high doses of *Mycobacterium leprae*. In Nepal, excellent survival of nude mice has been reported in a clean room without special isolators. *M. leprae*-infected nude mice are being used as models for chemotherapeutic and immunologic studies. Other work has utilized neonatally thymectomized Lewis rats and congenitally athymic rats.

Renewed efforts to utilize primates as models of leprosy have been successful. Naturally occurring leprosy has been reported in a sooty mangabey monkey. The animal, captured in West Africa and subsequently suspected of having leprosy, was further investigated and the diagnosis confirmed. Histologically the lesions were of the sub-polar lepromatous type of leprosy. The AFB found in large numbers were indistinguishable from *M. leprae* by the available parameters of identification. The organisms from this monkey were passaged to 2 mangabey monkeys, 2 rhesus monkeys, 3 African green monkeys and 3 squirrel monkeys. Inoculation was by intravenous as also intracutaneous routes except in one rhesus monkey which received only intracutaneous inoculation. The dose inoculated was of the order of 10^9. The mangabey, the rhesus and the African green monkeys developed leprosy within 2 years. The rhesus monkey inoculated intracutaneously and the squirrel monkeys did not develop the disease. Human (armadillo adapted) *M. leprae* were inoculated to mangabey, rhesus and African green monkeys. The mangabey monkey showed evidence of dissemination of disease in 10 months. No manifestations of the disease were evident in the rhesus and African green monkeys at 28 months.

K V DESIKAN, *Chairman*
R C HASTINGS, *Rapporteur*

Microbiology

1 ANIMAL SOURCES OF BACTERIA

Colonies of infected nine-banded armadillos are established in several countries. The nu/nu mouse is a promising alternative.

2 PURIFICATION

The IMMLEP 1/79 process yields antigenically intact bacteria with some adsorbed host material (removable by further processing). Methods using density gradients, including unit gravity sedimentation, have been described; the products have been less well characterized.

3 STRUCTURE AND ULTRASTRUCTURE

The capsular material around *Mycobacterium leprae* is ultrastructurally and chemically distinct from that around organisms of the MAIS group. The plasma membrane differs from that of other mycobacteria, since the leaflets seem symmetrical. Polysaccharide-specific stains give a characteristic appearance.

4 CHEMICAL STRUCTURE

Four types of characteristically mycobacterial lipid occur in *M. leprae*: mycolic acids, phthiocerol dimycocerosate, phenolic glycolipid and tuberculosteric acid. The glycolipid is serologically active and apparently antigenically unique; it is a major capsular component.

5 MOLECULAR BIOLOGY

DNA has been isolated from *M. leprae*. The genome size is in the mycobacterial range, but its G+C ratio is significantly low. Hybridization confirms that the organisms from experimental and 'natural' armadillo infection belong to the same species. Homology with other mycobacterial species is reported to be in the range of from 7 to 26%; homology with some corynebacteria is from 20 to 28%.

Although the whole genome is thought to have been cloned in *E. coli*, no expression has been detected.

The organisms will bind some types of mycobacteriophage but there is no evidence for multiplication.

6 ANTIGENICITY

Mycobacterium leprae possesses specific antigens and common mycobacterial antigens perhaps including one of ribosomal origin. Cell clones recognize antigenic determinants of mycobacteria that do not conform to conventional taxonomy. At least two different immune-suppressor activities have been recognized in other mycobacteria and these may be present in *M. leprae*.

7 BIOCHEMISTRY

Uptake of DOPA or incorporation of thymidine by suspension, or incorporation of thymidine in macrophage culture, has been used to screen drug sensitivity (and also viability). Measurement of ATP content is a sensitive measure of the metabolic state of organisms.

Uptake of glucose, amino acids and other potential nutrients occurs.

Glycolysis, the pentose–phosphate pathway and the tricarboxylic acid cycle appear to operate in *M. leprae*.

Nucleic acid synthesis uses 'salvage' pathways, as in some protozoan parasites. Many individual enzyme activities have been detected and distinguished from host-derived activity. Superoxide dismutase is present but catalase has not been detected.

8 CULTIVATION

Three types of organisms have been cultivated from infected tissues: i, mycobacteria; ii, corynebacteria resembling human pathogenic corynebacteria; iii, morphologically variable organisms with some acid-fast forms.

Type i has been reported to change its properties, especially effects on cells, during subculture. Traces of serologically active glycolipid have been detected. Type ii has been well characterized in biochemical terms. An improved culture system has been described for type iii. None of these much resembles *M. leprae* isolated from tissues.

9 PROSPECTS

The leprosy bacillus grown *in vivo* emerges as a mycobacterium-like organism with several curious features. Its metabolic processes are understood in outline and several measures of viability are, or are being, developed. The prospects for cultivation of organisms having identical properties seem good.

P DRAPER, *Chairman*
S R PATTYN, *Rapporteur*

Workshop report on immunology of leprosy

Major advances made in the past 5 years in the understanding of immune responses in leprosy were discussed. Though universal agreement on mechanisms underlying the unresponsiveness in lepromatous leprosy was lacking, interesting *in vitro* studies indicated that several suppressive mechanisms were operative. One study showed that *Mycobacterium leprae* and phenolic glycolipid induced OKT8(+) T cells capable of suppressing mitogen responsiveness were present in lepromatous individuals. Their activity was reversed by chemotherapy and immunotherapy with BCG+ killed *M. leprae*. Other studies reported diverse membrane-associated alterations in blood-borne macrophages of lepromatous patients and 75% familial contacts. These changes were specific for *M. leprae* in the patient group. Fc, HLA-DR and Con A receptors were found to be diminished and macrophage lysates inhibited lymphocyte responses. Moreover,

LL monocytes inhibited antigen-induced lymphoproliferation through the release of soluble factor(s). The inhibitory factors were heat stable, indomethacin resistant and were greater than 25,000 molecular weight. Macrophage lysates, monocytes and monocyte-released soluble factors from LL patients inhibited antigen-induced lymphoproliferation. Production of gamma interferon, a macrophage activating factor was found to be reduced in lepromatous patients. However, LL monocytes were capable of responding to it in microbiocidal assays. Interleukin 1 (lymphocyte activating factor) production in response to *M. leprae* was found to be normal but interleukin 2 (T cell growth factor) was not detectable in lepromatous leprosy. Interestingly, antigen responsive lymphocytes were also observed in some lepromatous patients. Addition of exogenous IL 2 along with *M. leprae* restored proliferative responses and reversed the gamma interferon defect. Similar data was obtained in C57 BL mice infected intravenously and subcutaneously with *M. lepraemurium*. Moreover, murine T cell clones induced by *M. leprae* were shown to produce IL 2, macrophage activating factor, gamma interferon and proliferative responses and to induce delayed hypersensitivity reaction, bactericidal and tumourcidal activity. The T cell clone technology in analysing immune mechanisms in leprosy was further emphasized. Alteration of T cell subsets as well as the characterization of immune complexes in erythema nodosum leprosum and reversal reactions were reported. Moreover, *M. leprae* antigens were recognized in the immune complexes and a possible defect in their handling in reactional patients was postulated.

An important advance has been the detection and characterization of *M. leprae* antigens in several laboratories. A unique phenolic glycolipid present in *M. leprae* and not in other related mycobacteria has been characterized and partly synthesized. Leprosy patients have been shown to have mainly IgM and IgG antibodies to this antigen. Chemotherapy reduced antibody titres but immunotherapy with BCG + heat killed *M. leprae* had no effect. Healthy individuals and tuberculosis patients did not show antibodies to the phenolic glycolipid. In addition, protein and glycoprotein of 12 KD antigens specific for *M. leprae* were described. A skin test antigen which measures 24 h delayed hypersensitivity is also being characterized. Specific monoclonal antibodies against the glycolipid and protein antigens have been developed. Possible tests for the early diagnosis of leprosy and for immuno-epidemiological studies were discussed. ELISA, radioimmunoassay and indirect immunofluorescence against several *M. leprae* antigens are being tested in the field. Concomitant skin tests and tests for presence of antibodies may help in the identification of high risk groups in the community. Such tests would be of value in not only understanding the disease, but in screening for future vaccine trials.

The feasibility of developing immunoprophylaxis and immunotherapy for leprosy was indicated in three studies. *M. leprae* BCG, ICRC and *M.W* and acetoacetylated *M. leprae* are being investigated in Venezuela and India. Some 50–70% lepromatous patients showed conversion from negative lepromin

reactivity to positivity status, and developed reversal reactions. Skin biopsies revealed upgrading of tissue reaction and bacillary clearance of significance was the conversion of 90% of lepromin-negative healthy individuals to lepromin positivity with all of the above preparations.

In order to generate alternative sources of production of *M. leprae* antigens libraries of *M. leprae* DNA cloned in *E. coli* have been made in the USA and India. Recent studies on the relationship of *M. leprae* Schwann cells and axons in nerve damage associated with leprosy were presented. One study also showed a deficiency of zinc and alterations in Langerhans' cells in LL patients. An association between HLA DR2 and tuberculoid leprosy has been confirmed. Furthermore HLA MT1 has been shown to be associated with lepromatous leprosy in one study. A general improvement of cellular immunity and immunoregulatory T cell function by a synthetic thymic factor was reported in experimental models and human disease.

The understanding of inverse relationship between genetically controlled natural resistance to primary attack by live mycobacteria and the ensuing disease and cell-mediated immunity in mice were discussed. Preliminary data found in human leprosy seems to indicate analogous mechanisms. Several of the above studies suggest that lepromatous population is heterogenous in its restoration of responsiveness *in vitro* as well as after specific immunotherapy. Such differences in the population as well as genetic and environmental factors need to be precisely defined for future strategy for the control of the disease.

G P TALWAR, *Chairman*
P H LAGRANGE and
INDIRA NATH, *Rapporteurs*

Experimental chemotherapy

During the past 5 years, awareness has been heightened of the threat to leprosy control posed by drug resistance, especially resistance to dapsone. Secondary resistance to dapsone has been recognized wherever it has been sought. Moreover, organisms with a low degree of resistance to dapsone have been encountered in as many as 50% of patients with previously untreated lepromatous leprosy. Although these patients should nevertheless respond to treatment with dapsone in full dosage, this observation suggests an alarming situation.

The increasing prevalence of dapsone-resistant strains of *Mycobacterium leprae* requires that all multibacillary patients be treated with a combination of drugs. In addition to rifampicin, clofazimine and ethionamide or prothionamide, other well-tolerated bactericidal drugs are urgently needed. One of the major requirements for the development of new drugs is appropriate, *in vitro* methods for screening large numbers of compounds for activity against *M. leprae*. A

number of methods are currently being evaluated. For example, '*M. lufu*' is being used in the search for inhibitors of the dihydrofolate reductase of *M. leprae*. In addition, advances in our knowledge of the biochemistry of *M. leprae* may provide leads to other target enzymes.

The ubiquity of poor drug compliance emphasizes the importance of using drugs that are effective when administered intermittently under supervision.

Persistent *M. leprae*—i.e. drug-susceptible organisms that survive prolonged treatment by adequate chemotherapy—have been detected in significant proportions of patients treated by a variety of multidrug regimens, among them regimens consisting of rifampicin, dapsone and clofazimine or prothionamide, each drug administered continuously in full dosage for 2 years. This suggests that no multidrug regimen is likely to eliminate persisting *M. leprae*. On the other hand, it is not certain that cure of multibacillary leprosy requires that all of the persisting organisms be killed. An 8-year follow-up of more than 300 multibacillary patients released from control after 20 years of well-supervised monotherapy with dapsone in full dosage yielded a relapse rate of only 1% per year. Among more than 100 multibacillary patients who had been treated with 2 years of intensive multidrug therapy after dapsone monotherapy of variable duration, no relapses were noted during a follow-up of 8–9 years. Thus, the use in leprosy control of intensive multidrug treatment of limited duration appears justified. Mathematical modelling may permit a more detailed understanding of the dynamics of the multibacillary patient's bacterial population during chemotherapy.

L LEVY, *Chairman*
ELEANOR STORRS, *Rapporteur*

Workshop on epidemiology and leprosy control

Significant progress has been achieved in our understanding of the epidemiology of leprosy since the last International Leprosy Congress. This has resulted in striking changes in the classical strategy for leprosy control which was previously based on dapsone monotherapy.

1 EPIDEMIOLOGY

i *Magnitude of the problem*. There has been no appreciable change in the global estimates of leprosy during recent years.

ii *Transmission*. The importance of airborne spread as one of the methods of transmission of *M. leprae* has gained wide acceptance. The viability of *M. leprae* outside the human host for at least 10 days has now been firmly established. The

role of paucibacillary cases in the transmission of *M. leprae* has not yet been clarified. Similarly, the importance of finding AFB in the nasal mucosa and skin of individuals with no clinical disease, poses the question of the carrier state in leprosy and requires elucidation.

Mycobacteria indistinguishable from *M. leprae* have been identified in the environment. Isolation of similar organisms from animals, with or without a leprosy-like disease, raises the question of host specificity of *M. leprae* to man.

iii *Immuno-epidemiology*. Significant advances have been achieved in the development of immunological tools for the recognition of *M. leprae* infection. The FLA–ABS test, the ELISA technique using phenolic glycolipid antigens and inhibition assays based on monoclonal antibodies deserve special mention. Recent studies with currently available tests provide strong presumptive evidence that the incidence and prevalence of *M. leprae* infection far exceeds clinical leprosy in endemic areas. Availability of a sensitive and specific test feasible under field conditions to identify *M. leprae* infection, is an urgent requirement for the proper understanding of the epidemiology of leprosy and the effects of control measures.

iv *Genetic factors*. Data on family segregation analyses of HLA, provide evidence of some genetic involvement in tuberculoid and perhaps also lepromatous disease response. Further studies are required in this direction.

v *Drug resistance*. Secondary dapsone resistance has been reported from more than 25 countries and its prevalence is steadily increasing. Primary dapsone resistance is also being reported with increasing frequency from several countries. Similarly, there have been reports of *M. leprae* showing resistance to rifampicin and to other drugs.

Indicators of declining trends

Indicators of declining trends have now been identified by studies from Norway, Japan, the Philippines and Venezuela, based on the fact that the decline in incidence rates has been paralleled by a change in the distribution of age at onset towards older age groups. The usefulness of such indicators needs to be further evaluated.

2 LEPROSY CONTROL

i *Multidrug therapy*. Two threats to the successful implementation of the classical strategy for leprosy control are the widespread emergence of dapsone-resistant strains of *M. leprae* and the problem of persistence of bacilli. The best way to prevent the spread of dapsone-resistant leprosy is to use multidrug

therapy. Only 4 drugs can be recommended for combined therapy, namely rifampicin, clofazimine, dapsone and prothionamide/ethionamide. In 1981 the WHO Study Group on the Chemotherapy of Leprosy for Control Programmes recommended combined therapeutic regimens for the treatment of both multibacillary and paucibacillary leprosy.

While this workshop endorses the principles underlying the use of multidrug therapy in leprosy, based on the WHO recommendations, it also recognizes the fact that the schedules adopted by different countries vary in detail. All regimens need to be evaluated with special emphasis on relapse rates, occurrence of reversal reactions, side-effects of drugs and operational feasibility. Reactions should be clearly distinguished from relapses in such evaluations. The workshop recommends the development of a simple serological test to monitor the success of treatment.

ii *Strengthening of the infrastructure.* It is now essential to perform bacteriological examinations and to classify patients correctly, since drug regimens are different for multibacillary and paucibacillary leprosy patients. The critical factor will be the flexibility of the treatment delivery system which should be tailored to meet the individual needs of patients. Continuity, regularity and completion of chemotherapy will be the keys to the success of the new strategy. The logistics of drug availability and their supply to the periphery and the retraining of staff to cope with their increased responsibilities need to be adequately strengthened. Regularity of treatment, completion of treatment and duration of surveillance should be defined in the context of implementation of multidrug therapy. Patients should be considered to have completed treatment, if they have taken 6 supervised monthly doses, within a period of 9 months in paucibacillary leprosy, and 24 supervised monthly doses, within a period of 36 months in multibacillary leprosy. It is also recommended that surveillance should be continued for at least 2 years for paucibacillary patients and for 5 years for multibacillary patients, after completion of the course of treatment.

A patient who has been absent for 1 calendar year may be considered to be 'out of control'.

iii *Information system.* A suitable recording, reporting and information support system, based on the OMSLEP pattern, should be designed and used. The information requirements at various levels of the health care delivery system must be explained to the personnel so that the reasons for the collection of data become meaningful to them. Completeness of case ascertainment should be an area of priority, and special attention must be given to the problems of under-reporting and multiple registration. Simple and robust indicators for epidemiological surveillance and operational monitoring of control programmes should be developed and applied. It is recommended that whenever statistics are quoted, they should include a precise description of their derivation. It is further

recommended that patients on treatment be considered separately from those under surveillance.

iv *Primary health care approach*. In endemic areas, with integrated health services, the full resources of the primary health care delivery system must be mobilized to implement and support the programme, so that its optimal potential can be put to maximum utilization. Every effort must be made to promote community involvement. The key factor in the primary health care approach is its focus on the consumers of the health care system. Practical methods to promote awareness and generate community involvement need to be identified, through field oriented studies.

v *Urban leprosy control*. In the endemic countries, increasing urbanization has resulted in the emergence of leprosy as a major public health problem in towns and cities. Prospective planning should therefore emphasize the formulation of urban leprosy control programmes so as to meet the challenges that lie ahead.

vi *Primary prevention*. Non-availability of an effective and practical method of specific protection has been a major impediment in the control of leprosy. Although moderate efficacy of chemoprophylaxis with dapsone and acedapsone has been established under trial conditions, mass chemoprophylaxis is not operationally feasible in a service programme. However, in this context, chemoprophylaxis with a single dose of rifampicin needs to be investigated.

An armadillo-derived killed *M. leprae* vaccine has been shown to confer protective immunity in animal models. Its evaluation in humans is now being undertaken through small-scale studies. Vaccines derived from related mycobacteria are also being developed. It will, however, be several years before accurate information regarding the efficacy of these vaccines can be established.

M CHRISTIAN, *Chairman*
B NAAFS, *Co-Chairman*
J P MULIYIL, *Rapporteur*

Teaching and training

INTRODUCTION

Prior to the workshop, it was agreed to focus on the selection, production and distribution of books and pamphlets for leprosy control workers. There were 4 reasons for this:

1 Appropriate literature is still by far the most influential source of new information and ideas.
2 Books do not require any elaborate apparatus for their effective use.

3 Books are relatively cheap to produce and distribute.
4 Really good and appropriate written learning material can make a great contribution to the effective training of the large numbers of health workers who will become responsible for leprosy patient care in integrated and primary health care programmes.

However, the participants of the workshop were also aware that much of the reading material available is not entirely appropriate and that distribution of appropriate literature is very patchy.

AIMS

The aims of the workshop were as follows:

1 To prepare a short list of current titles in English appropriate for various categories of health staff.
2 To identify gaps in existing literature in English.
3 To prepare similar lists of material available in languages other than English, especially in major international languages.
4 To outline proposals for further development of effort to produce, distribute and assess material for leprosy workers.

PROCEEDINGS

Based on previous work done primarily by INFOLEP in Amsterdam and The Leprosy Mission (International) in London and the varied experience of the workshop participants, short lists of books in English appropriate for 6 broad categories of workers were prepared and a number of important gaps and deficiencies in the literature were identified. Due to limited time and lack of full representation, it was decided not to attempt to do the same for other languages at this time.

The second day of the workshop was taken up with the presentation (by participants) of field experience in production, distribution and utilization of learning materials in a variety of situations at the central and peripheral levels. This was followed by a sharing of AMREF experience in East Africa in line production and distribution of learning materials in the field of general health by Dr Christopher Wood. Extensive and frank discussion intensified the exchange of information and ideas.

CONCLUSIONS

A great variety of literature exists in English and with a few exceptions can potentially meet the need of most workers who can read that language with reasonable fluency. There are, however, 3 areas where improvement is essential:

Much of the existing literature could be made more useful by simplifying the language and improving presentation.

2 Distribution leaves much to be desired: many workers are not even aware of the existence of literature which could help them and the present system for distribution of material often fails to deliver literature to those who need it.

3 Many students and workers have little or no skill in the use of literature as an aid to learning for basic or continuing formal or non-formal education.

It is apparent that there is a serious shortage of readily available material in languages other than English, especially for paramedical workers. Translation of existing English material is one way of coping with this situation. But translation of technical material is not easy, and translations, even by experts in linguistics, should be checked for technical accuracy by people familiar with both the language and the subject matter.

RECOMMENDATIONS

1 The contribution of appropriate learning material to the competency and motivation of workers should be recognized and funds for literature should be provided as an essential item in every leprosy control programme.

2 Efforts to collect and disseminate information about literature in languages other than English should continue.

3 Assessment and subsequent improvement of existing material in English should in general have priority over production of new material in that language.

4 Efforts to provide learning material for field workers in local languages should be intensified since there is a notable lack of literature for this particular group.

5 Training in the use of written material should be an integral part of basic and refresher courses for all staff.

6 Effective distribution of literature, especially to staff at the periphery, is as important as the distribution of drugs and should be given similar priority.

W F ROSS, *Chairman*
A C McDOUGALL, *Rapporteur*

Social aspects

1 POLICY STATEMENT

The aim of social research in leprosy should be to assist in improving the policy and execution of leprosy control. At the same time, it should contribute to a conceptual framework which helps to understand the social, economic and psychological problems experienced by leprosy patients, their relatives and health staff concerned.

2 CRITERIA FOR RESEARCH

(a) Research should be scientifically sound, ethically acceptable and cost-effective.
(b) Research should be carried out by interdisciplinary teams of social, medical and, if appropriate, economic scientists.
(c) The active participation of local personnel (medical, paramedical, social workers), as well as patients and community members should be encouraged.
(d) Research should preferably be undertaken by national researchers who meet the required qualifications.

3 RESEARCH TO DATE

Research to date has concentrated on the following topics:

(a) Knowledge, beliefs and attitudes concerning leprosy and health-related behaviour of leprosy patients and community members. Often research results are geared to health education.
(b) Social, economic and psychological consequences of contracting leprosy, namely stigma, and their relationship to rehabilitation.
(c) Patient compliance: medical, social, economic, cultural, psychological and leprosy service factors influencing case-finding and case-holding.
(d) Management and functioning of leprosy control: health staff's knowledge of leprosy and leprosy treatment, and its behaviour towards leprosy patients; organizational bottlenecks in leprosy services; cost-effectiveness, e.g. of vertical services, of integrated services, and of primary health care including leprosy control.

These topics have been elaborated in a number of meetings organized by WHO and national/international leprosy associations.

4 PROPOSALS

This working group strongly encouraged a *comprehensive approach* to problems in leprosy control, paying equal attention to factors related to the patient, his near surroundings and to the leprosy services. *Research should ultimately concentrate on those areas where problems are most obvious and where remedial action seems most feasible.*

The following topics were proposed for elaboration:

(a) Definition by community and patients of the concepts of illness and cure in leprosy:
Terminology of different manifestations/stages of leprosy used by community and patients.

(b) Stigma:
Possible differences between perception of stigma by community members and patients, and the degree of stigma actually experienced.
Forces that make some leprosy patients stigmatize themselves (comparative research).
Mechanisms that help patients to maintain and regain their social and economic position in society; determinants of self-acceptance and community acceptance of patients.

(c) Evaluative research of:
Acceptability to patients, community and health staff of different types and ways of providing services.
Content and impact of health education.
The possible contribution of community, leprosy patients and social services to leprosy control, including care of the handicapped.
Economic and social consequences of reconstructive surgery.

(d) Participation in the planning and monitoring of trials with multidrug therapy; evaluation of the effect of MDT on community and patient perceptions of leprosy.

(e) Participation in planning, monitoring and evaluation of vaccine trials in the field.

(f) Investigation of factors in human behaviour which may be contributing to transmission of leprosy, e.g. migration.

5 RESEARCH METHODS

A combination of research methods should be used: study of relevant documents; informal and formal interviews; questionnaires; systematic observations.

Questionnaires as a single research tool may give superficial and misleading results.

6 IMPLEMENTATION OF RESEARCH RESULTS

Social research should provide direction for possible solutions to problems, as well as alternative proposals for action.

The results should be presented in terms which are understandable to the potential users.

Implementation of research results will be more effective if the social scientists who conducted the research are invited to participate.

In order to increase the quality and quantity of social research and its impact on leprosy control, it was suggested that regional centres be developed as focal points for collection and dissemination of research results. These centres would

also develop training programmes for social research in leprosy and carry out investigations.

The manual on *Social Dimensions of Leprosy* (published by ILEP, 1982) was discussed in the workshop. This book could be useful to paramedical teachers who have some training in social sciences and who can adapt it for local use.

In order to be useful at the field level, the theoretical part needs considerable revision and focussing on the working situation of field staff.

CORLIEN M VARKEVISSER, *Chairperson*
F GIRARDIN, JUDITH JUSTICE
and PATRICIA ROSENFIELD, *Rapporteurs*

Lepr Rev (1984) **55,** 206–210

Topics in leprosy

EIGHT SLIDE AND VIDEOTAPE PRESENTATIONS

A new and outstandingly important development at the Congress in Delhi was the use of slide-text and videotape topics for teaching. These were held in different rooms throughout the Congress and they were extremely well attended. English, French and Spanish versions were available. The following topics were selected for the slide presentations:

Immunology. New understandings of the immunology of leprosy and introduction to current terminology, techniques and concepts.
2 *The eye.* The recognition and management of the ocular manifestation of leprosy.
3 *Reactions.* The recognition and management of reactive phenomena and of neuritis.
4 *Nerve damage and rehabilitation.* The pathophysiology of nerve damage and deformity and the clinical management of disability and anaesthetic limbs.
5 *Epidemiology and control.* Approaches to leprosy control and therapy in the field, programme planning, supervision, implementation and evaluation.
6 *Public education.* Education of the public and of patients in leprosy, principles, plans and practices.
7 *'Case taking'.* Clinical examination and smear taking leading to clinical description and diagnosis.
8 *Classification.* The delineation of clinical and histological types in leprosy, using the new Indian classification.

Format. The material is available in print, on audio cassette tape, 35 mm slides and videotape. The latter includes Betamax and VHS formats and PAL and NTSC systems. Videotape is also available in $\frac{3}{4}$ format by special order.

Ordering. Copies may be ordered from American Leprosy Missions, Inc, One Broadway, Elmwood Park, NJ 70740, USA. Costs are as follows: A Slides and script, $16.00; B Slides, tape and script, $20.00; C Videotape/Betamax/NTSC, $20.00; D Videotape/VHS/NTSC, $20.00; and E Videotape/VHS/PAL, $20.00. Prices include air mail postage and all items are available in English, French and Spanish.

A summary of the main content of each title reads as follows:

Leprosy Immunology—Present State of the Art by Tore Godal

The host's immune response to antigens of the leprosy bacillus is of key importance to several clinical manifestations of the disease:

(a) Towards the tuberculoid end of the spectrum, the disease is expressed mainly by a delayed type hypersensitivity (DTH) and granuloma formation.

0305-7518/84/055206+05 $1.00

(b) Studies both in experimental animals and patients suggest that nerve damage in tuberculoid and borderline patients results from DTH reactions against *Mycobacterium leprae* antigens in nerves.

Another area of intense research is the nature of the immunological defect in lepromatous leprosy (LL). Most recent studies suggest that suppressor cells and deficiencies in T-cell growth factor production are involved in failure to control *M. leprae* multiplication. Thus, evidence continues to point to a defect in the T-cell compartment. Further studies in this field should help in constructing rational immunotherapeutic approaches in LL. The lack of specific antigens from *M. leprae* has put a constraint on progress in immunoepidemiology. New techniques such as monoclonal antibodies, T-cell cloning and recombinant DNA technology provide promising new avenues in this field. These methods will also be of great importance in identifying protective antigens and for designing vaccines produced *in vitro*. Nevertheless, armadillo-derived *M. leprae* has shown promising features in experimental animals and has reached a stage of clinical trials.

The programme will focus on the above-mentioned areas outlined in simplified terms and the new techniques now applied to leprosy and indicate some avenues of leprosy immunology during the next decade.

The Eye in Leprosy by Margaret Brand

Blindness, although not the most common complication of Hansen's disease, is one of the most distressing and feared by the patient.

The eye lesions in advanced disease are often complex and may baffle experienced ophthalmologists. But they do not become so overnight. They begin as simple conditions, often easily recognizable with the help of a good pen-light and magnifying loupe, which can be reversed if detected early.

In the slide presentation the various aetiologic factors are demonstrated. These are summed up as follows:

1 Motor nerve damage. Lagopathalmos. Patient wants to close the eye but cannot.
2 Sensory nerve damage. Patient could close the eye but, being unaware of dryness or other painful conditions, does not do so. Factors 1 and 2 may operate together. Corneal damage then becomes a strong possibility.

To a varying degree all types of HD are subject to factors 1 and 2.

3 Mycobacterial infiltration of anterior segment structures, the iris, ciliary body, cornea and sclera.
4 Inflammatory reaction, the ocular counterpart of erythema nodosum leprosum.
5 Damage to neighbouring extraocular structures: skin—lacrimal system.
6 Secondary infection.

An awareness and recognition of these factors simplifies diagnosis and makes successful management a hopeful outcome. Better yet is to prevent their onset by good case-finding, case-holding and careful attention to the eyes from the beginning.

The Recognition and Management of Reactive Phenomena and of Neuritis by R St C Barnetson

The leprosy bacillus is unique in several ways: one very interesting property is its lack of toxicity. Lepromatous leprosy patients may have 10^{12} organisms within their tissues without any clinical manifestations. The most important complications of leprosy result from immunological hypersensitivity phenomena known as leprosy (lepra) reactions. In some parts of the world, clinicians regard all reactions as having the same pathogenesis, which is unfortunate as the two main types of reactions and erythema nodosum leprosum may be treated very differently.

Borderline leprosy reactions are a common cause of major nerve destruction, and are due to an

increase in delayed hypersensitivity. If the patient is treated early and with adequate doses of steroids then permanent nerve damage can be avoided. Erythema nodosum leprosum results from immune complex formation, and may be accompanied by arthritis neuritis, iridocyelitis, orchitis and nephritis: if it is frequently recurrent then permanent damage may result. Prevention by the use of clofazimine, thalidomide and steroids make long-term complications less likely.

Nerve Damage and Rehabilitation by Paul Brand

Most of the complications of leprosy that result in permanent disability and stigma are due to the damage to peripheral nerves.

If patients are to recover completely from the effects of the disease it is necessary: 1, to minimize damage to nerves; 2, to compensate for paralysis; and 3, to prevent damage and destruction to limbs that have lost sensation.

In this slide set the cause and pattern of nerve loss is explored, and methods of prevention outlined.

Surgical rebalancing of the limbs is advocated but not detailed.

The damage to insensitive hands and feet is seen to be due to:

(a) Penetrating injuries from sharp objects and burns that destroy the skin.
(b) Sustained pressure from tight shoes or straps which destroy skin by keeping it bloodless for hours at a time.
(c) Repetitive stress on parts of the foot that take most of the thrust of walking, and repetitive stress on parts of the hand that hold the handles of tools. This constant repetition may result in inflammation and then blister and breakdown. It is often worse because of pre-existing paralysis or deformity that exposes just one or two parts to stress.
(d) The most severe damage is caused by continuing use of a limb that is wounded. The importance of special footwear, splints and plaster casts is emphasized.

Epidemiology and Control by M F Lechat

This series on epidemiology and control reviews the present strategy of leprosy control and the epidemiological rationale which underlies it. After presenting the magnitude of the leprosy problem in the world, and the main epidemiological indices used, i.e. prevalence and incidence, the potential methods of leprosy control are critically discussed: segregation, chemoprophylaxis, chemotherapy, and possibly in the future, vaccinations. Their advantages and drawbacks are reviewed.

Leprosy control at present is based on early detection of the patients as a source of infection and negativation of the reservoir through chemotherapy. The organizational aspects of this strategy are presented, together with present constraints and requirements. The consequences of drug-resistance, with the resulting need for multiple therapy, are given particular emphasis. The ultimate aim of integrating leprosy control into primary health care, with full participation of the community, is stressed.

Health Education for Patients and Public in Leprosy Control by P Jane Neville

This audio-visual production is based on the work of the Leprosy Control Unit at the Richardson Hospital, Miraj, Maharashtra, India. It is one of the 23 leprosy control units staffed by The Leprosy Mission in India.

The presentation was filmed with the staff as they carried out an intensive health education campaign prior to the introduction of multidrug therapy. The viewer is stimulated to ask 3 important questions about the health education campaign: 1, How is health education planned? 2, How is it carried out? (methods and media); and 3, What are the results? (evaluation). The terms

'health education' and 'health information' are often confused and an attempt is made to differentiate between these two terms. The presentation sets out to identify factors which seem to be important for the success of health education not only in this project but in other projects as well.

The viewer is shown not only the health education activities which are an integral part of the Miraj Leprosy Control Unit, but is also introduced to the theory behind an educational campaign. This is done by means of diagrams, sketches, tables and cartoons, as well as photographs.

'Case Taking' in Leprosy by K Ramanujam

Leprosy, in the majority of instances, lends itself for diagnosis on the basis of a proper clinical examination alone. Hence it is mandatory that a set pattern is followed in the examination of an individual for the presence of leprosy. This procedure is known as 'Case taking' in leprosy.

The prerequisites for undertaking this procedure are: to remember that leprosy is no respecter of persons; awareness of the occurrence of leprosy in the community, especially in areas where leprosy is endemic; a pair of observant eyes; an unbiased mind; an attitude that will never take things for granted; and lastly, familiarity with the early manifestations of leprosy and the clinical signs of the disease.

'Case taking' consists of:

1 Interrogation. (i) Collection of biodata of the individual such as name, age, sex, occupation and place of residence; (ii) family history of leprosy; (iii) history of contact with cases of leprosy; (iv) details of previous treatment for leprosy, if any; and (v) presenting complaint or symptom.
2 Clinical examination. (i) Inspection of body surface, to the extent permissible, in good natural light for the presence of suggestive or tell-tale evidences of leprosy; (ii) palpation of the commonly involved peripheral and cutaneous nerves at the sites of predilection for the presence of thickening and/or tenderness; and (iii) testing for evidence of damage to the sensory or motor component of the peripheral nerve, such as: (a) sensory changes in the skin, patches, or the peripheral parts of the limbs, and (b) paresis or paralysis of the muscles of the hands and feet leading to disabilities or deformities.

The 'Case taking', as far as possible, should be supplemented by the taking of smears from the skin and the nasal mucosa by standard methods and examining for the presence of *Mycobacterium leprae*. This will enable the detection of the very early lepromatous cases which, otherwise, will be missed.

Clinical and Histological Types by K V Desikan

In view of the variegated clinical manifestation of leprosy, classification of the disease is extremely important. Also the presentation of the disease has certain peculiar clinical features in different countries. It is therefore necessary to have a system of classification which would be fully representative of the clinical pattern of the disease in India. Secondly, several categories of workers are engaged in the study of leprosy from the basic field worker to the highly academic research scientist. A classification therefore should have basically a uniform approach to workers of all levels. Thirdly, the classification should be simple and essentially clinical, not depending on the need for sophisticated investigations. A new classification of leprosy worked out by Indian leprologists aims to fulfill the needs mentioned above. The new classification is a five group classification. While there is no confusion regarding the polar types of leprosy, a peculiar feature of leprosy in India is the occurrence of a large proportion of cases with flat or macular lesions. The new Indian classification defines the clinical, bacteriological and histological features of these lesions to assign them to their proper place. Another important group of cases frequently seen in India are the ones with pure neural involvement which have been assigned a separate group.

* * *

The following information is taken directly from the information sheet which accompanied the videotape programmes:

Mice Against Leprosy. Prepared by Dr J Almeida. Duration 10 min.
Painless Feet. Prepared by Dr E P Fritschi. Duration 15 min.

The above videotapes are available in VHS, Betamax and U-matic formats in the PAL System with English Commentary.

French and Spanish language versions will be produced if there is sufficient demand.

The price of each programme will also depend on overall demand. But it will probably be in the region of Rs 325, i.e. cost of a blank videotape and shipping.

Karigiri Video is based at the Schieffelin Leprosy Research and Training Centre, Karigiri-632106, Tamil Nadu, India.

The project was established in 1983 with the support of American Leprosy Missions and the Sasakawa Memorial Health Foundation to produce a comprehensive series of video programmes for training medical officers in leprosy.

It is staffed by professional production personnel and collaborates with the outstanding teachers in leprosy. About 12 programmes will be produced each year.

In addition to programmes for medical officers, Karigiri Video will be developing community education material and programmes for other health workers.

Karigiri Video will be available to produce special programmes on commission. Project director for Karigiri Video is Mr Michael Barnes.

For further details write to the above address stating which videotape you require, which PAL system and language you require together with your name and address.

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Post-congress workshops and seminars

Full accounts of these workshops will no doubt eventually be available for publication and at this stage it is only possible to give the following information:

1 Workshop on the Defective Macrophage in Leprosy, 27–28 February 1984

Venue: The Foundation for Medical Research, 84-A, R G Thadani Marg, Worli, Bombay, 400018, India

Further information from: Dr N H Antia, The Foundation for Medical Research, 84-A, R G Thadani Marg, Worli, Bombay 400018, India.

Resource personnel: 1, Staff of the immunology division of FMR. 2, Invitees participating in the seminar.

'The immunology division of the Foundation for Medical Research was one of the first groups to initiate studies on the role of macrophage in the immune defect in leprosy. Since 1976, extensive work has been carried out in assessment of *Mycobacterium leprae*-induced alterations in the macrophage membrane, characterization of macrophage-derived suppressor factors and genetic control of macrophage susceptibility of *M. leprae*. The results demonstrate a central macrophage defect in leprosy and have provided new means to evaluate immunomodulating agents and anti-leprosy drugs.'*

2 Workshop on Health Education in Leprosy, 27–28 February 1984

Venue: Gandhi Memorial Leprosy Foundation, Hindinagar, Wardha, Maharashtra 442103, India.

Further information from: Mr S P Tare, Gandhi Memorial Leprosy Foundation, Hindinagar, Wardha, Maharashtra 442103, India.

Resource persons: Mr S P Tare, Director; Prof. R K Mutatkar, Head, Department of Anthropology, University of Poona, Poona, India.

* For those attending this meeting in Bombay, Dr Antia and his colleagues (T J Birdi, P R Mahadevan, N F Mistry and P R Salgame) produced a comprehensive review on *The Defective Macrophage in Leprosy* with the following main headings:

Ch. I, 'The role of the macrophage in a normal immune response', pp. 1–11; Ch. II, 'Parasite survival mechanisms within the host', pp. 12–21; Ch. III, 'The immune defect in leprosy', pp. 22–40; Ch. IV, '*M. leprae* induced alterations in the macrophage', pp. 41–102; Ch. V, 'Evidence for an inherent susceptibility to *M. leprae* as reflected in the macrophage', pp. 103–57; Ch. VI, 'An overview', pp. 158–74; Ch. VII, 'Applications derived from monitoring of macrophages *in vitro* functions', pp. 175–92; 'References', pp. 193–208.

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3 Seminar on Foot Care, 6 March–9 March 1984

Venue: Philadelphia Leprosy Hospital, Salur, Vizianagaram Dt, Andhra Pradesh 532591, India.

Resource persons: 1, Dr P W Brand (Carville); 2, Dr E P Fritschi (Karigiri).

4 Seminar on Eye Problems in Leprosy, 6 March–9 March 1984

Venue: Philadelphia Leprosy Hospital, Salur, Vizianagaram Dt, Andhra Pradesh 532591, India.

Resource persons: 1, Mrs Margaret Brand (Carville); 2, Staff of the Ophthalmic Unit, Philadelphia Leprosy Hospital

Further information from Dr Alexander Thomas, Superintendent, Philadelphia Leprosy Hospital, Salur, Vizianagaram Dt, Andhra Pradesh 532591, India.

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Miscellanea

Amongst the many treasures included in the leather conference bag presented to each delegate on registration were the following:

The Programme of the XII International Leprosy Congress, 1984 with full details of all events from the pre-Congress workshops to the closing session. The opening pages describe the foundation of the International Leprosy Association and list the previous congresses, beginning with that held in Berlin in 1897 to the last which was in Mexico in 1978.

The Abstracts, a strongly bound paperback of over 200 pages, listing all the 510 papers accepted under the following headings: Clinical Aspects; Immunology; Treatment; Microbiology; Surgery and Rehabilitation; Rehabilitation; Ophthalmology; Nerve Damage; Experimental Leprosy; Epidemiology and Control; Experimental Therapy; Pathology; Social Aspects.

An address list of the official delegates, an invaluable and absolutely up-to-date record of the family names, initials and addresses of all those attending.

The Souvenir of the Congress, with 'keynote' articles as follows: 'The Organizing Secretary's Report' by Dr R H Thangaraj; 'The XII International Leprosy Congress', by Dr K V Desikan (Editor); 'The International Leprosy Congress Comes to be Held in India' by Dr Dharmendra; 'National Leprosy Eradication Programme in India' by Dr K C Das; 'Leprosy Work in India by Voluntary Agencies' by Mr S P Tare; 'Gandhi Memorial Leprosy Foundation' by Mr S D Gokhale; 'The Leprosy Mission: Southern Asia at a Glance'; 'Report on the Activities of the Leprosy Mission in Southern Asia' by Dr R H Thangaraj; 'Training Programmes in Leprosy' by Dr R K Sengupta; 'Leprosy Research in India' by Dr K V Desikan and Dr U Sengupta.

Atlas of Leprosy, produced by the Sasakawa Memorial Health Foundation, Tokyo, Japan. This superb atlas of leprosy is a successor to the 'loose-leaf' format produced some years ago, and reviewed in this Journal. The patients are from Cebu in the Philippines and virtually all manifestations of leprosy are covered in a series of colour prints of outstanding quality. There is now a section on differential diagnosis and also on the histopathology of leprosy.

* * *

***NLO*; National Leprosy Organization of India.** This 59-page booklet describes in considerable detail the origin, objectives, policy, development and current activities of the NLO and lists over 80 member institutions. Beginning with the Acworth Leprosy Hospital in Bombay this valuable source of information goes on to describe the main activities of its members in widely scattered parts of India, including programmes in rural, urban and slum settings. Read in conjunction with the above-mentioned account of the National Leprosy Control Programme, this booklet gives a most valuable insight into leprosy work in India generally.

***Future*; a quarterly from UNICEF, India.** This 1983 issue of 16 pages, under the title of 'Development Perspectives on Children' carried a leading article on community development in Anandwan, Somnath and Hemalkasa in the Vidarbha region of the State of Maharashtra, based mainly on a visit to Baba Amte, this year's winner of the Damien–Dutton Award, and Dr Vikas Amte in Anandwan. Considerable attention is given to the way in which such centres have welcomed people who would usually be considered outcasts, including those suffering from leprosy.

UNICEF: *Leprosy Control: Everyone's Concern*; United Nations Children Fund Regional Office for South Central Asia, New Delhi-110003. This 45-page booklet was written specially for the Congress and the closing paragraph of the Introduction summarizes its objective:

'A breakthrough can come through a change in the knowledge, attitudes and practices of society, and in particular of various influential groups including of course, the health personnel. This publication is intended to promote the process of such change. It is addressed to different segments of society—the health profession, the education system, voluntary agencies, the media, the policy makers and the general public. It is hoped that the discussion that follows will stimulate the reader to make his or her own invaluable contribution to leprosy control.'

Chapters following are: 'Towards Eradication' by K C Das; 'Community Action' by K V Desikan; 'The Medical Role' by R H Thangaraj; 'Effects of Education' by M S Nilakanta Rao; 'Voluntary Work' by S P Tare; 'Leprosy and the Law', by S P Tare; 'Communication for Control' by R Ganapati; 'Gandhi on Leprosy'. An Annex carries a list of voluntary organizations engaged in leprosy control.

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ILEP Meeting on Multidrug Therapy (MDT)

On the Sunday preceding the opening of the Congress, an all-day meeting on MDT was organized by ILEP (The International Federation of Anti-Leprosy Associations, 234 Blythe Road, London W14 0HJ), during which preliminary reports were presented from workers in various parts of the world, who have already implemented MDT. Many of them have already been invited to submit accounts of their experiences in this important area of activity for possible publication in this Journal in 1985.

We are indebted to the Secretary to the Medical Commission, Dr H W Wheate for the following account of the Meeting.

Morning session

The Chairman, Mr A D Askew, opened the Meeting by welcoming all present and asked them to introduce themselves.

He pointed out that MDT offered a great opportunity for advance in leprosy control because it was not only a tool to combat dapsone resistance, but also was necessary only for a defined, limited period of time. It must, however, be applied properly and this Meeting between field workers and members of ILEP had been arranged to discuss the practical problems of implementation of MDT. It was hoped that field workers would explain what they expect from the Voluntary Agencies, which in their turn, would discuss the managerial aspects which are their particular concern.

The result of the Meeting should be practical recommendations.

REPORTS

1 *Ethiopia*—Dr Marijke Becx-Bleumink

The progress achieved in the pilot programme initiated in one area has been affected by several problems. The preparation prior to implementation of MDT had, it was subsequently realized, been inadequate. The technical guidelines for the staff were published only after the programme had started. Previous clinical records had been on the whole poor in quality and smear examinations were generally not done. It had taken time to deal with all these problems, but now they were also ready to start in the area around Addis Ababa.

In the discussion, Professor Pattyn pointed out that it is more important to do skin smears in cases clinically diagnosed as paucibacillary than in those obviously multibacillary. It was also pointed out that after the prescribed period of 6 months' chemotherapy, the skin lesions would still be active in some patients. The fact that chemotherapy is no longer indicated under these circumstances will call for considerable skill in patient management and explanation.

2 *Malawi*—Dr G Boerrigter

Dual therapy with rifampicin and dapsone had been in general use for multibacillary cases since 1981 and the staff capable of giving supervised drugs was therefore available.

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One problem was the backlog of large numbers of paucibacillary patients who no longer needed chemotherapy and in many cases the solution was 'the golden handshake of 6 months' MDT'.

Since 1981, they had experienced no side-effects resulting from the use of rifampicin given in 2 doses of 600 mg on successive days (the first supervised, the second to be taken at home the next day), but there had not been a controlled study.

A system of surveillance had been developed. It was pointed out that this was a vertical programme and that therefore implementation was probably easier than in integrated programmes. A practical recommendation was that a careful check should be made in cases with a BI of around 2+.

In the discussion, it was pointed out that this programme illustrated the value of proper preparation of both staff and patients. One delegate enquired if cases of fainting after rifampicin had been noticed and Dr Gjalt said that such cases had occurred. The occurrence of reactions after completing the 6 months' period of chemotherapy in paucibacillary cases was also noted. It was agreed that 50% of relapses in paucibacillary cases are likely to occur within 3 years and that thereafter surveillance should be limited to asking patients to report back themselves if they notice anything untoward.

3 *Niger*—Dr A Cissé

A pilot project to test the feasibility of the WHO regimens under local conditions is in the course of implementation. There are 500 patients under treatment, 425 paucibacillary and 75 multibacillary. Seminars are held for all health staff of the general health service.

Shortage of trained supervisory staff is however a problem. The programme of health education of the public seems to be effective in increasing public awareness of leprosy and ensuring that patients are welcome to the health centres providing treatment. One interesting feature was a modification of the WHO regimen to take account of local conditions—in the dry season, the monthly supervised drugs are given, whereas in the rainy season when supervisory visits are impossible, dapsone and clofazimine only are dispensed for unsupervised intake at home. Treatment is given on market days. One problem is that most of the population is illiterate and nomadic.

4 *Paraguay*—Dr A E Alvarenga

In this programme, a total of 789 patients had been treated by Isoprodian. Of these, 30 had defaulted and 5 died, leaving 754 on the register, 553 multibacillary and 201 paucibacillary.

To date, 293 multibacillary and 192 paucibacillary cases had been discharged from chemotherapy, and so far there have been no relapses—the period of observation extended to 4 years in some cases. The average duration of treatment in multibacillary leprosy was 1 year 2 months. In the discussion, it was observed that the period of treatment was not fixed, in order to find out the optimum duration of therapy. This involved, however, difficulty in assessing relapse rates. Side-effects had been minimal; 155 patients complained of gastrointestinal disturbances and one with hepatitis had to suspend treatment.

5 *Miraj, Maharashtra, India*—Dr P D Samson

The programme covered a population of 250,000 and was organized through paramedical workers each covering 5–6 villages with a population of about 25,000.

Before introducing MDT, there had been a year of careful preparation, including 1 week's initial training for all the staff, followed by a 'refresher' for 2 days per month, the formulation of 10

key indicators to evaluate operational efficiency, especially as to attendance and case detection. There was also a programme of health education involving firstly the patient and his family, and secondly development officers, group leaders, as well as the news media, village meetings and posters.

The regimens adopted were modifications of the WHO Recommendations. The dapsone intake was monitored by urine testing (the Tile Test) and tablet counts. The plan of operation was based on a routine timetable for the month—1 week of survey, 1 week of pre-clinic preparation and follow-up, 1 week of treatment distribution and 1 week of administrative routine.

The cost amounted to Rupees 343 per patient or approximately Rupee 1 per head of the population covered. There had been no serious side-effects among any of the patients treated who included 191 over the age of 50 years and 101 children.

Two features of this programme particularly noted during the discussion were the importance of health education and the provision for domiciliary rehabilitation.

6 *Tamil Nadu, Uttar Pradesh and West Bengal, India*—Dr Claire Vellut

The regimen adopted is a modification of that recommended by WHO and includes an initial period of intensive therapy with daily rifampicin for multibacillary cases.

It had been found that importing additional staff for the implementation of MDT made for difficulties in subsequent follow-up. Preliminary Health Education had been found to be essential for success—as in Miraj.

The attendance rates were better than with dapsone monotherapy, possibly because patients were impressed by the care taken with their clinical examination before starting treatment and by the emphasis on the initial period of intensive therapy in multibacillary cases.

Afternoon session

The Chairman, Dr D S Chaudhury, explained that this session was to be devoted largely to discussion of the practical implementation of MDT including such matters as preliminary planning, the encouragement of patient compliance, the training of staff, monitoring and evaluation, the identification of the human and social needs of the patients, and cost effectiveness. We were not in a position to discuss the effectiveness of the various drugs used and should preserve an open mind on this issue. He then asked Dr Cap to present his paper, the text of which is given at the end of this article.

Mali—Dr Nebout

The situation was unlike Niger with its Primary Health Care Programme. Coverage by basic health services was inadequate and mobile units were required. The planning of the MDT programme took account of the need for the training of the staff in techniques of clinical and bacteriological examination and their clear job description, the management of drug distribution, criteria for discharge and health education.

Ivory Coast—Dr Serie

Attention was focused on the problem of urban leprosy in cities like Abidjan where stigma seriously affected early self-presentation.

DISCUSSION

The main points covered in a wide ranging discussion were:

1 The fact that the cost of the drugs required for MDT amounted to only 10–20% of the total cost of the programme and that the major expenditure is on operational costs, drug delivery, etc.

2 Whereas Voluntary Agencies are free to choose a particular drug regimen, Governments have to adopt the minimum effective in order to reduce transmission.

Their priority must be to detect and treat all infective cases and they cannot therefore be so concerned about possible relapse rates. There is a need for agreements between Governments and Voluntary Agencies.

3 The phrase 'minimum effective regimen' needs emphasis. This implies the optimum therapy to prevent disability—which is the whole *raison d'être* of leprosy control.

4 Planning must include identifying the problems before MDT is introduced and much money spent. The staff, especially the supervisory staff, need to be trained and prepared (some may fear that the new treatment policy threatens their job). A programme is only as good as the staff it employs.

5 There must be a built-in monitoring procedure based on a well-designed recording and reporting system, with valid operational indicators. In addition, there is need to define the minimum standards of training, of infrastructure, etc., at regional and national level required before MDT should be applied. Voluntary Agencies can then provide funds for countries or projects where minimum standards have been achieved. This will involve support beyond those projects already being financed, and may include assistance to create the essential infrastructure. There is a close link between underdevelopment and leprosy.

The Chairman closed by formulating the following conclusions which were endorsed by the Meeting:

CONCLUSIONS

As multidrug therapy is a very important intervention in our fight against leprosy, it is absolutely imperative that adequate and in-depth planning is made before multidrug therapy is introduced in any area.

2 Such planning must be adapted to the local situation and should ensure minimum effective service which depends upon appropriate information on the disease problem and sufficient and correct documentation. This can be facilitated through visits of experts and meetings between the project manager and senior field workers.

3 Multidrug therapy programmes must have an in-built system of monitoring based upon competent reporting and objective analysis.

4 Correct laboratory control is an essential item to evaluate the programme. The staff should be appropriately trained and updated in this field.

5 Introduction of multidrug therapy in no way precludes our giving full attention to the needs of the individual patient and his family. Discharge from therapy does not mean discharge from care.

6 Health education is extremely important to ensure early diagnosis and maximum compliance by the patients, both in taking the drugs as well as in limb care—including care of the eye. The programme of health education must run parallel to the other activities of the programme.

7 Community participation will promote the success of multidrug therapy and will help in the rehabilitation and social reintegration of the patient. Multidrug therapy programmes must involve the community at all effective levels.

8 Unless all these prerequisites are obtained, multidrug therapy should not be implemented in haste or in a lighthearted manner.

Paper presented by Dr Cap at the XXXth Working Session of ILEP to the Interface Meeting on the Introduction of Multidrug Therapy, Athens, December 1983.

'. . . It is my opinion that we have no choice: MDT has to be introduced because of the constant increase in secondary and primary dapsone resistance. Its application will also shorten the duration of the treatment, with, hopefully, a beneficial effect on patient compliance. Furthermore, it will reduce the period of infectiousness of multibacillary cases, producing a faster decrease in the incidence rate.

Mr Askew's paper[1] is a very valuable and welcome contribution. It emphasizes the need for assessing the possible effect of MDT from a managerial point of view. It is obvious that these managerial aspects will have to be confirmed by medical assessment and a study of suitable parameters for evaluation is being taken up by the Medical Commission. It also points out that the cost of the drugs, though not negligible, does not represent the main obstacle to introducing MDT, the success of which depends upon an adequate medical infrastructure.

As a matter of fact, from a technical point of view, the introduction of MDT is a very difficult exercise, with a number of constraints, some of which have already been stressed in the ILEP booklet[2]. As we all know, in several endemic countries, the situation is not yet sufficiently ripe to introduce MDT on a sound basis, with regard, for example, to basic competence of the staff, operational requirements and so on.

We would like to review the most practical points which could help us to make use of MDT in a proper way, avoiding to do more harm than good.

We should, first of all, be aware of the fact that the number of effective drugs is very limited and that there is no reasonable hope of having additions to the actual list in the foreseeable future. Several specific or other vaccines are in the making, but it will be many years before toxicity and feasibility studies are completed and many more again before their efficacy has been defined and before they can be used safely and widely in endemic areas.

The WHO working group which met in October 1981 has proposed treatment regimens for paucibacillary and multibacillary patients. These regimens are rightly considered as minimal and nothing less should be administered, but they should be applied in the most rigorous way. Even though these regimens are relatively simple, their practical administration will have to be adapted to local circumstances, differing from one country to the other.

These principles are expressed in the WHO[3] and in the ILEP[2] documents, but there is a need for strict, locally acceptable protocols, prepared with the assistance of a leprosy expert, containing detailed, locally adaptable procedures. Such protocols must be very detailed and cover not only the technical aspects, but also take related aspects into consideration, such as geographical constraints, record-keeping systems, administrative implications, requirements for extra staff, cars, etc.

If necessary, the protocol should be supplemented by a local manual for the staff, defining all decisions to be taken and covering all circumstances and doubtful situations which may arise in the particular area. It is encouraging to see that already several of such manuals have been produced, which may serve as a guideline for the elaboration of other manuals adapted to other and different situations.

Before introducing MDT, a thorough training of the staff involved will be essential, and in several areas training alone will not be sufficient. Their total attitude towards the problem of leprosy control has to be changed, and they must be convinced that the introduction of MDT means a revolution in the management of leprosy control programmes. This change of attitude concerns all levels of staff, including, and even more specifically, the medical officers in charge of projects.

In addition, patients must be educated, motivated and encouraged to take the full course of

treatment as prescribed. Preliminary reports from the field indicate that compliance to MDT may sometimes be better than has been the case in general with dapsone-monotherapy, and it must be our constant concern to make sure that this is always the case.

Training must definitely include staff in charge of laboratory examinations. The bacteriological index (BI) has always been of great importance in leprosy control programmes, though it was often rather neglected. With the introduction of MDT, the bacteriological index becomes essential in making extremely important decisions. Strenthening of the laboratory facilities and training of the staff are therefore essential, so that the needs, as defined in the protocol, can be met both quantitatively and qualitatively.

In many areas, it will be necessary to start application of MDT in a selected area where the essential requirements can be met and where the practical, sometimes unexpected, snags and constraints can be identified.

Before introducing MDT, it is important to review all patients still on the register. In many areas, patients, mainly paucibacillary cases, remain on the register for many years for several reasons: partly because in the past the criteria for defining inactivity were unclear, and partly because dapsone was cheap, safe and easy to use, so that it was often continued unnecessarily. Under MDT, the protocol must be strictly observed, as the drugs involved are more expensive and more toxic.

It is obvious that a well-oiled drug supply and distribution system has to be set up. This problem has been a quite simple one during the dapsone monotherapy era. We now have to deal with expensive, relatively toxic drugs with a limited shelf life. Regular supplies and correct distribution at the right time are therefore of the utmost importance.

Finally, it is important to learn from the experience of our colleagues in tuberculosis who have found that the correct managerial handling of diagnosis and treatment presents major difficulties in the control of tuberculosis and we can surely expect that the same will apply in the control of leprosy.'

References

[1] Askew AD. (International Director, The Leprosy Mission—Nov. 1983). *Effects of MDT on Leprosy Programmes.*

[2] *Introduction of Multidrug Therapy for Leprosy.* ILEP—June 1983.

[3] *Chemotherapy of Leprosy for Control Programmes.* Report of WHO Study Group Technical report series 625—WHO 1982.